Does Hormone Replacement Therapy Benefit Cognition in Elderly, Postmenopausal Women: A True or Mistaken Association?

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ABSTRACT

Hormone replacement therapy (HRT) has been studied as a protective factor for cognitive decline and dementia. However, study findings have been inconsistent. Variation in study findings may be due to differences in study designs, small sample size, exposure ascertainment, diagnostic procedures, and inclusion of relevant risk and confounding factors. Moreover, there may be significant differences between the characteristics of women choosing to use HRT and those opting not to use the therapy.

Using a large-scale, population-based, cohort study, we examined the relationship between HRT and cognition while paying particular attention to moderating and confounding factors. The main outcomes of interest were to assess differences in risk for cognitive impairments and dementia between HRT user and never user groups; examine HRT's impact on age of onset of dementia; and explore the relationship between duration of HRT and cognitive decline. Logistic regression and Cox Proportional Hazards models were used to test HRT as a predictor for cognitive impairments, Alzheimer's disease and vascular dementia, as well as to assess the effect of duration. Linear regression was used to consider the putative relationship between age at onset of dementia and HRT status. HRT use was found to be a statistically significant predictor for Alzheimer's disease and vascular dementia. Overall, HRT use did not significantly predict for milder cognitive impairments, although significant interaction effects indicate that HRT may be protective at least for specific sub-groups of women. No durational effect was found for any of the outcomes. Neither did HRT appear to predict for age at onset of dementia. Notably, a large proportion of women in the current study reported using estrogen-only hormone supplements, and therefore generalizations regarding the findings are likely limited to estrogen-only preparations, not combination estrogen-progestin therapies. These findings must be considered within the context of the other known and potential risks and benefits that HRT may afford.

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DEDICATION

To my parents, Barbara and Gordon, and my siblings
for their endless love, support, and enthusiasm.

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Seniors are one of the fastest growing population groups in Canada. As the population ages, the number of people with cognitive impairment and dementia-related illnesses will markedly increase. With this growth, Canada can expect an increased social and economic burden resulting from the intensified need for health care services, long-term care facilities, and the cost of both formal and informal caregiving. Because the effects of dementia on our society are far-reaching and health reform is focusing on cost-containment, the need for immediate interventions and effective treatments is evident.

In 1994, the *Canadian Study of Health and Aging* (CSHA) prevalence estimates suggested that 252,600 Canadian seniors (8%) met the criteria for dementia (1). Each year there will be approximately 60,150 new cases of dementia in Canada – 36,320 will be women and 23,830 will be men, and 46, 670 will occur in the community and 13, 480 in institutions (2). The occurrence of dementia-related illness is not randomly distributed throughout the senior population. Jorm demonstrated an age-related increase in the prevalence of dementia, doubling approximately every 5 years after age 60 (3). A large portion of the older adult population is at risk for developing this illness in their lifetimes.

At the individual level, dementia sufferers are at an increased risk for poor health and mortality (4). Though estimates of survival range from 5 to 9.3 years, after accounting for length bias, Wolfson et al. (2001) report a mean survival of just 3.3 years following the onset of the disease (5). In a five-year follow-up study, after a diagnosis of possible or probable AD, only 21% of individuals survived (5). While there is no known cure for dementia, research efforts are aimed towards understanding the

mechanism of dementia and possible interventions that will delay or prevent the progression of this illness.

More women than men, of all ages, are diagnosed with dementia. The female: male ratio is 2:1(6). In terms of Alzheimer's disease (AD), women are 2-3 times more likely than men to develop this illness after age 70 (7). Initially, it was believed that the differential gender distribution might be due to women's longer life expectancy. However, life-table studies have suggested that higher risk of AD in women is not solely due to greater longevity (8). This suggests the possibility of an alternative explanation for the increased number of cases of dementia in women. There may be a gender-specific variable, such as postmenopausal estrogen levels, impacting the progression and development of dementia in women.

Research has indicated that pre-clinical cognitive deficits exist prior to the discernible clinical onset of dementias such as Alzheimer's disease (AD) (9-11). The picture emerging is that some dementias such as AD are characterized by early declines in a variety of cognitive areas and that these declines persist over time. Labels such as "mild cognitive impairment", "age-associated memory impairment", and "cognitive impairment no dementia" have been used to depict this pre-clinical phase of impairment.

In the CSHA, "cognitive impairment no dementia" (CIND) is a broad category used to classify cognitive impairments that do not meet dementia criteria for a range of reasons including, but not limited to, severity (12). CIND is broken down into many sub-types based on the cause of impairment, such as those due to chronic alcoholism, visual or auditory impairments, psychiatric illness, vascular disease, and socio-cultural factors. Furthermore, a distinction was made between CIND and "cognitive loss no dementia" (CLoND). CLoND is used when participants with either CIND or "no cognitive loss" (NCL) experience significant loss in cognitive functioning between study phases, but still do not meet the criteria for a dementia diagnosis (13). A CIND diagnosis is thought to increase one's risk of developing dementia in the future, whereas the importance of the CLoND classification in determining dementia susceptibility is not yet known.

Cognitive Impairment No Dementia (CIND) is twice as common as dementia in seniors and is independently associated with functional disability and increased risk of mortality (14). In CSHA, the prevalence of CIND was 16.8% (15). After five years, 47% of participants with CIND progressed to dementia, while only 15% of individuals who were cognitively normal at baseline developed the disease (16). When enhanced treatment options are discovered, CIND will be an important marker to identify when therapy should begin (17). For this reason, CIND is an important component of dementia-related research.

Hormone replacement therapy (HRT), particularly estrogen, has been studied as a protective factor for cognitive decline and dementia. However, the findings have been inconsistent. The benefits of estrogen on women's health are known, but there is debate as to whether these benefits outweigh the risks. Estrogen has been found to exert a wide range of effects on the reproductive system, cardiovascular system, skeletal system, and neuronal systems serving cognitive functions, especially memory (18). There are several plausible mechanisms through which estrogen might benefit cognition (19), both in the short and long-term. If HRT is found to protect women from dementia, or to delay the onset of this illness, this would reduce the time spent with disability, and lengthen and improve quality of life. Chapter 2 provides an up-to-date review of the current literature on HRT use.

The goal of this thesis work was to examine the role of HRT in cognition and cognitive decline, while paying particular attention to moderating and confounding variables reported in the literature. Data was used from the first and second wave of a large-scale cohort study, the *Canadian Study of Health and Aging* (CSHA). The CSHA has followed the physical, mental, and social health of seniors (65 years and older) throughout Canada over a 10-year period. Because of its large and representative sample (n=10, 263), stringent diagnostic process, and longitudinal nature, the CSHA offers a unique opportunity to study HRT as a protective factor for CIND and dementia. Understanding the relationship between HRT and cognition is highly important to health professionals, researchers, and women in general. This thesis adds to the literature by reconciling a number of the methodological problems that limit the validity of previous study conclusions, thereby strengthening confidence in research on this

topic. Once the effects of HRT are more accurately known, women will be able to make more informed decisions regarding the use of this particular therapy. And, as Henderson points out, "considering the distressingly high prevalence of AD among older women and the exorbitant social and economic costs associated with this disorder, a true risk reduction would be of tremendous public health importance" (19).

1.1 Study Hypothesis

HRT use protects postmenopausal women from developing cognitive decline and impairments (CIND, CLoND, AD, and VaD). However, the strength of this association will be biased if risk and confounding factors are not controlled for in analysis.

1.2 Objectives

The objectives of this thesis were to determine:

1. If the characteristics of HRT users differ from those of never users.
2. If there is an increased diagnosis of cognitive impairment no dementia (CIND), Cognitive Loss No Dementia (CLoND), Alzheimer's disease, or vascular dementia in women never using HRT as compared to HRT users.
3. If HRT use is a significant predictor for CLoND, CIND, Alzheimer's disease or vascular dementia.
4. If the age of onset of dementia is earlier in women never using HRT than in women who have used HRT.
5. If there a dose-response relationship between HRT usage and CIND, CLoND, AD and vascular dementia.

While examining the relationship between HRT and cognition, known risk factors for dementia such as age, education, income, NSAID use, head injury, APOE-4 presence, lifestyle factors, environmental exposures, and chronic health conditions will be controlled for in the analyses. This will be done in an effort to ascertain HRT's true effect on cognition by adjusting for factors occurring to a greater or lesser degree in the user group.

CHAPTER 2: LITERATURE REVIEW

2.1 Important Concepts

Estrogen Replacement Therapy:

Estrogen replacement therapy (ERT) has been prescribed for decades as a means of treating the symptoms of menopause by using estrogen to stabilize declining hormone levels in women. Because of the increased cancer risk associated with its use, it is now usually only given to women with a hysterectomy who are not at risk for endometrial cancer. There are two types of ERT, natural and synthetic, which are distinguishable by their chemical composition (20). Each type of estrogen and the form it is administered through (eg. pill, patch, cream) has different absorption characteristics, with oral forms increasing total plasma estrogen levels more than vaginal creams (21). Estradiol, estrone, estriol, and their conjugates, as well as conjugated equine estrogens are all natural estrogens that are used in ERT (20); while ethinyl estradiol, mestranol, quinesterol, diethystilbesterol, and raloxifene are included in the synthetic class (20). Although there are many types of ERT, Premarin ™, or conjugated estrogen, is the most frequently prescribed preparation today (20).

Hormone Replacement Therapy:

Hormone replacement therapy (HRT) is the combination of both estrogen and progesterone in the form of a pill, patch, cream, gel, injection, implant or vaginal ring. The addition of progestins was a response to growing evidence that estrogen alone may promote cancers of the reproductive tract. With the addition of progestins, the transformation of ERT into HRT hoped to circumvent earlier discovered negative health consequences, such as endometrial cancer. However, the progestins added have been linked to an increase risk for breast cancer (22).

For simplicity, the term HRT will be used when referring to all types of hormone therapy. Notably, estrogen-only preparations have been used most frequently

in the past and by women with a hysterectomy, but in recent years combination therapies are becoming increasingly common.

Menopause:

Menopause is the time following a woman's last menstrual period. A woman must go 12 consecutive months without her period before she is said to be in menopause. In Western industrialized countries, the median age at menopause is currently 50 years of age (23), although the age of onset will differ greatly from woman-to-woman. In CSHA, menopausal status was determined by each participant, but was not directly included in analysis.

Dementia:

Dementia is a broad category that includes AD, vascular dementia, and other specific dementias. Approximately two-thirds of all dementia cases are due to AD, with vascular dementia being the second most common form(1). According to DSM-IV-TR, the most recent diagnostic criteria, a dementia diagnosis must include (24):

-multiple cognitive deficits including memory impairment, and at least one of:

-aphasia (language disturbance)

-apraxia (impaired motor activities despite intact motor function)

-agnosia (inability to recognize objects despite intact sensory function)

-disturbance in executive functioning (i.e. planning, organizing, sequencing)

Cognitive deficits must also:

-be sufficiently severe to cause impairment in occupational or social functioning

-represent a significant decline from a previously higher level of functioning

-not occur exclusively during the course of a delirium

In the CSHA, each dementia diagnosis includes a measure of severity. At the initial phase of CSHA, a three-point scale was used to specify the severity of dementia observed in each participant. From CSHA-2 forward, this is indicated by a rating on the Reisberg's Gobal Deterioration Scale (25). The scale has a range from stage 1 to stage 7, moving from cognitively normal to severe cognitive decline with interference in all activities of daily living (ADLs).

Alzheimer's disease (AD):

AD is an age-related and irreversible brain disorder that occurs gradually and results in memory loss, changes in behaviour and personality, and a decline in thinking abilities (26). It is a disease that belongs to the broader category of dementia. It is characterized by gradual onset and continuing cognitive decline; is not due to other conditions such as cerebrovasular disease, Parkinson's disease, hypothyroidism, vitamin B12 deficiency, nor is it substance-induced; and the disturbance is not better accounted for by another Axis I disorder such as schizophrenia or Major Depressive Disorder (24). In this thesis, I confine the discussion to late-onset AD where the incidence greatly increases with age, especially after 65 years.

Because most research on HRT and dementia is limited to AD, the most common form of dementia, a large portion of this thesis is focused on this specific type of dementia. However, HRT's effect on other dementias and CIND is an important and largely unanswered clinical question deserving attention.

Vascular Dementia (VaD):

Aside from AD, VaD is the next most common form of dementia. After a dementia diagnosis is made, it is determined whether or not there is a vascular etiology. For a diagnosis of VaD, there must be the presence of cerebrovascular disease (as demonstrated by history, clinical exam or neuroimaging) and it must be thought to be causally related to the dementia (27). There is, however, debate about the degree of overlap occurring between the AD and VaD pathologies (28).

Cognitive Impairment No Dementia (CIND):

A diagnosis of CIND is used for persons not meeting the criteria for dementia, but who have short or long term memory impairment and at least one of the following: impairment in abstract thinking, impaired judgment, disturbance of higher cortical functions (aphasia, apraxia, agnosia), or personality change (12). Similar to dementia, CIND is associated with increased risk for mortality and functional disability. Although research has not conclusively established its relationship to dementia, it appears that CIND may be an important precursor to disease development. Causes of CIND may fall into one of the following categories: delirium, chronic alcohol abuse, chronic drug intoxication, depression, psychiatric disease, mental retardation, cerebral vascular

(stroke), general vascular, Parkinson's disease, brain tumour, multiple sclerosis, epilepsy, socio-cultural, social isolation, blind/deaf, and unknown. As previously stated, CIND is a more general category of cognitive decline not meeting the criteria for dementia.

Cognitive Loss But No Dementia (CLoND):

During CSHA, CLoND was used to record declines from a previously higher level of cognitive functioning when the drop was not severe enough to be classified as dementia. The criteria for CLoND is assessed independently after it has been determined that the participant has either no cognitive impairment or CIND. It also must not occur exclusively during the course of a delirium (13). CLoND is used in an effort to identify more subtle changes (losses) in cognition from one assessment to the next.

2.2 Hormone Replacement Therapy (HRT)

Interest in HRT has been evident since the 1960s when physicians were already prescribing these drugs (29). In recent years, HRT use by postmenopausal women has become increasingly common. HRT is one of the most frequently prescribed medications for postmenopausal women in the United States and Canada (30). According to the 1994/95 National Population Health Survey (NPHS), approximately 22% of Canadian women aged 45 –64 reported using HRT following menopause (31). More recent estimates from the CCHS found that 4% of women ages 40 and over reported currently using hormones. Aside from its potential to reduce the acute symptoms of menopause, HRT is believed to offer women protection from many long-term illnesses. Interestingly, research findings on the health benefits are not conclusive, and often contradictory, creating concern about the mass prescription of this therapy.

In the short term, women may differ in their experiences with HRT. It may alleviate early menopausal symptoms – hot flashes, insomnia, irritability, urinary incontinence, vaginal dryness – as well as lead to unpleasant side effects such as weight gain, breakthrough bleeding, and breast tenderness. The compliance and continuation of HRT will differ from woman-to-woman, with breakthrough bleeding, expense, preference for the natural, and health concerns being some of the more common reasons

for discontinuing treatment (20). Often more women with a hysterectomy begin HRT treatment and continue for longer durations than women without.

Over time HRT is postulated to protect women from a variety of chronic health conditions. Osteoporosis, cardiovascular disease, colon cancer, and Alzheimer's disease are some of the health problems that are currently being investigated**.** Studies have shown HRT to be associated with a significant reduction in colon cancer (30% in ever users and 46% for recent use) (32, 33), morbidity and mortality from coronary heart disease (CHD) (34, 35), cardiovascular disease (36), and bone loss (23). Research findings such as these have stimulated the use of HRT as a preventative treatment for many age-related illnesses.

The protective effects of HRT have been publicized by the media and supported by physicians, thereby legitimizing its use. In 1996 alone, the popular press in Canada mentioned HRT 152 times (37). In a study by Parker Jones (2000) surveying 425 primary care physicians for women, most responded that HRT was extremely or moderately important in the prevention of osteoporosis (99%) and cardiovascular conditions (96%) (38). Regardless of physicians' endorsement of this technology, there are questions about the safety of HRT and its implications for women's health.

A recent study, *The Heart and Oestrogen-Progestin Replacement Study*, found a 52% increase in adverse cardiovascular events in the first year of therapy in patients with a history of heart disease who used HRT (39). Distressingly, some studies have also found HRT to increase a women's risk for breast, gallbladder, endometrial, and ovarian cancers, depending on the length of use and whether or not progestins have been added (40) (41) (42) (43) (44). Using individual data from a large meta-analysis (n=52,705), a group of investigators found no increase in breast cancer risk with HRT use for 4 years or less, although use for 5 years or longer was associated with a statistically significant increase (RR=1.35; 95% CI 1.21-1.49)(30). Although less common after the first year of use, venous thromboembolism has also been found to be more frequent in HRT users than non-users (23). Pre-existing health conditions, the duration of treatment and the preparation used may determine the health consequences and benefits postmenopausal women receive from hormonal supplements.

During the compilation of this thesis work, the Women's Health Initiative (WHI) stopped its *Estrogen plus Progestin Trial*, a sub-component of the larger study. The WHI is a large, double blind, randomized, placebo-controlled, clinical trial studying the effects of HRT on postmenopausal women over an eight-year period. As one of the largest and lengthiest clinical trials to date, this multi-centre trial found a 26% increase in breast cancer which caused the study to be halted (45). Furthermore, the combination hormone therapy resulted in a 41% increase in strokes, 29% increase in heart attacks, and a two-fold increase in blood clots of the legs and lungs (45). In terms of positive health effects, there was a 37% decrease in colorectal cancer and 24% fewer total fractures (45). These combined results led investigators to conclude that "the overall health risks of estrogen plus progestin therapy exceeded benefits" and "the risk-benefit profile found is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases" (p.15) (46). However, it should be noted that the increased breast cancer risk for each individual women participating in the study was small (>0.10% / year) (45). Recently, data obtained from the WHI on dementia and mild cognitive impairment found that general dementia risk doubled for women in the estrogen plus progestin group (47). At present, this is the first finding that HRT increases risk for dementia. No treatment effect was observed for Mild Cognitive Impairment (MCI). The risks and benefits of using estrogen-only hormone therapy in women who have had a hysterectomy are not yet known; this study is still being carried out by the WHI since no negative health consequences have been found as yet. Nonetheless, there is much uncertainty surrounding the benefits and risks associated with HRT use. Further research and consideration is necessary before this treatment should be endorsed by the medical community, a fact that is increasingly being recognized.

2.3 The Neuropathology of AD

In the past decade, our understanding of Alzheimer's disease and its development have advanced significantly. The neurodegenerative process leading to the onset of AD is complex and may be initiated many years before its clinical onset (48). As research into the etiology and pathology of AD accumulates, the knowledge

gained allows for new interventions that may delay or halt the progression of this illness.

Theories about causation and the development of AD involve a combination of genetics, environmental exposures, and neurological insults impacting on the brain's physiology (49). Multiple factors appear to play a role in AD. Prominent theories include four main premises: it is a result of aging; the processes may result from physical trauma, aggravated by genetic factors, which inhibit repair mechanisms; a pathology resulting from the accumulation of toxins; and an inflammatory process (49). It may be that no one theory can fully explain the AD process, but instead it is likely that many interrelated factors result in disease development (48).

The major neuropathological features of AD are deposits of amyloid plaques, intraneuronal neurofibrillary tangles, synapse loss and the death of neurons (48, 50). The presence of plaques and tangles are required for a definite diagnosis of AD (51). These may occur over 10 years prior to dementia expression (50). Plaques are complex extracellular deposits in the neuropil containing ß-amyloid, which is produced in normal cells by the ß-amyloid precursor protein (48). It is not known what causes the plaques to form. Still, plaque deposition can be affected in many ways indicating that there may be several different mechanisms leading to a final common pathology (48). ß –amyloid can have a toxic effect on brain functioning. It increases the vulnerability of neurons to other insults such as excitatory amino acids, glucose deprivation, and oxidative stress (52). Although the role of plaques in AD pathogenesis is still unclear, ß -amyloid is an essential process in AD but does not appear causative (50). These findings lend support for ß -amyloid as an important antecedent in AD pathology.

In addition to plaques, neurofibrillary tangles are bundles of long protein filaments in the cytoplasm of neurons (48) and are also a necessary condition for the development of AD. Tangles are a result of the abnormal processing of tau protein(s) (48). In AD tau is chemically modified, and this changed tau twists into paired helical filaments, which then combine to form neurofibrillary tangles (26). This change may result in malfunctions in communication between nerve cells and then contributes to neuronal death and the development of dementia (26). Even though tangles are dispersed throughout the brain in AD patients, they are particularly concentrated in the

structures associated with memory processing (48, 53). The duration and severity of AD are directly correlated with the numbers of neurofibrillary tangles and synapse loss (48, 53).

The final characteristic of AD pathology is synapse loss and cell death. Plaques and tangles may both contribute to neuronal and cellular death (26). Synapse loss and neuronal death affects multiple neurotransmitter systems leading to multifaceted presentation of symptoms in AD patients (54), but the nucleus basalis of Meynert, the source of cholinergic function, and the septal nucleus, which provides cholingeric innervation to the hippocampus are particularly affected (55, 56). For this reason, many therapies for AD aim to improve acetylcholine function (48), including widely used drugs such as donepezil and rivastigmine. Rather than being separate pathologies, it's likely that plaques, tangles, synapse and cell loss are part of a complex, interrelated process imperative to the way that the brain ages and copes with damage (48).

Because AD's neurodegenerative process may take decades to unfold (48), any interventions slowing or preventing the production of tangles and plaques, and subsequent synapse loss and cell death, would be of great consequence. Current therapies operate by slowing the disease's progression, but do not reverse the damage already done. If HRT fosters neurological functioning and acts in a preventative manner, its use following menopause may be highly significant to women's cognitive health and quality of life.

2.4 HRT's Mechanism of Action

It is thought that ovarian factors are important to the normal maintenance of brain function in women, and therefore the time after menopause is critical to cognitive health(54). In recent years, HRT has been studied extensively as a protective factor for cognitive health. It has been shown to modify many of the factors contributing to the neurodegenerative process, although much of the evidence relating to a mechanism of action has been obtained through animal studies (57).

Studies have found endogenous estrogen levels to be lower in postmenopausal women with AD than in women without dementia (58). Although the mechanism by which HRT protects cognition is not yet fully understood, many plausible theories are being validated by recent research. Honjo (2001) suggests a combination of four

mechanisms to explain the beneficial effects of hormone therapy (59). These include improved mood leading to better test performance on cognitive screens; vascular dilation in the CNS making neurons more active; activation of acetylcholine metabolism, including the hippocampus and the hypothalamus; development of glia, which helps neurons in the CNS (59). HRT is also believed to have anti-inflammatory properties and to mediate the negative impact of ApoE-4 on the brain (26). Because of estrogen's important biological role, it is possible that it affects many of the processes eventually leading to the development of dementia.

The declining estrogen levels that accompany menopause may initiate or accelerate neuropathological processes. This neurodegenerative transformation may be slowed through HRT's actions. HRT is believed to attenuate the adverse effects of ß-amyloid, thereby preventing plaque formation. For instance, one study found that cerebrospinal fluid levels of estrogen were significantly lower in AD patients than in controls; within the AD group estrogen levels were inversely correlated with ß -amyloid concentrations, providing evidence for an influence of estrogen on ß -amyloid metabolism (60). It is also suggested that estrogen may decrease production of ß -amyloid and help to concentrate it into focal deposits, although it is not found to be effective in actually clearing ß -amyloid (61).

Estrogen has both anti-inflammatory and antioxidant effects. Conjugated estrogen has been found to antagonize inflammatory damage triggered by ß–amyloid peptide (62, 63), a response which may be similar to the protective effects of non-steriodal anti-inflammatory drugs (NSAIDs). Moreover, the excess production of free radicals, which occur during normal metabolism, causes oxidative stress that can injure cells and result in damage (26). The reported antioxidant properties of estrogen might attenuate oxidative damage induced by ß–amyloid (64). Once ß -amyloid accumulates as plaques, estrogen treatment seems to make little difference in the brain.

Not only is estrogen a factor in reducing plaque formation and lessening ß -amyloid's inflammatory and oxidative stress, but it may have a significant effect on neurotransmitter systems. Estrogen is able to restore plasma acetylcholine transferase levels in postmenopausal women (65). Acetylcholine is considered the most important neurotransmitter involved in the modulation of memory, learning, and cognitive

function (23). Patients with AD show a marked decrease in the activity of choline acetyltransferase, an enzyme involved in the synthesis of acetylcholine in the cerebral cortex and hippocampus (6). Other neurotransmitters possibly involved in the AD process, such as noradrenaline, seretonin, dopamine, and norepinephrine are also affected by estrogen (63, 66).

Estrogen's neuroprotective role seems to operate not only through neuronal, but also vascular actions. MRI was used to document ischemic brain injury in 210 postmenopausal women for ten years (67); the 70 women taking ERT in this study had fewer and smaller damaged areas than the 140 controls. Improving cerebrovascular function is considered a viable option in AD treatment, as many vascular abnormalities are observed in AD patients (57). Estrogen may also effectively improve cerebral blood flow, although study findings have been inconsistent (57).

Often AD is conceptualized as an imbalance between neuronal injury and repair (50). Evidence suggests that estrogen not only decreases the risk of dementia through the suppression of the neurotoxic stimulus itself, but lessens the extent of injury sustained by increasing the resilience of the brain to a given injury (68). Estrogen stimulates production of nerve growth factors, thereby promoting neuronal growth and viability, repair of damaged neurons, and dendritic branching (63). Through estrogen's actions, HRT may play a role in repairing the damage that would otherwise lead to AD and other dementias.

Importantly, once the damage is present in the brain, HRT might be less effective in treating dementia. HRT seems to be more effective in the initiation phase of neurodegeneration rather than just prior to clinical onset (69). Hence, if estrogen is deemed beneficial, it should be used earlier on for the primary prevention of dementia for the most favorable outcome.

2.5 ApoE and Dementia

Recent epidemiological studies have shown ApoE to be an important genetic risk factor for AD and other dementias. The CSHA found that seniors with any copies of the ApoE-4 allele were almost three times more likely than those without to develop AD (70). It has been suggested that HRT may ameliorate the detrimental effects of ApoE-4 on cognitive decline.

ApoE is a protein with three common alleles – ApoE-2, ApoE-3, and ApoE-4. All people have two copies of this protein, which may include different alleles (heterozygous versus homozygous). In a study of the Canadian population, the allele frequencies were reported to be 7.8% (E2), 77.0% (E3) and 15.2% (E4) (71). The E3 allele is the most common in the general population, however approximately 40% of AD patients have the E4 allele (72). This overrepresentation of the E4 allele in persons with AD suggests a role for ApoE as a genetic risk factor in the AD process.

As a component of various lipoproteins, including very-low-density-lipoproteins (VLDL) and a subset of high-density lipoproteins (HDL) (73), APOE is a critical modulator of cholesterol and phospholipid transport between cells (74). It is essential for the repair, growth, and maintenance of membranes that occur during development or after injury (71, 75, 76). As an injury response protein, ApoE may transport cholestrol and other molecules to the injured neurons to be used in repair, with the E4 allele being less effective in this process (50). Therefore, ApoE may influence the impact that head injuries and other environmental toxins have on the brain, and on subsequent development of cognitive impairment. For instance, the risk of developing AD with a history of head trauma was increased up to ten times in E4 carriers compared to non-carriers (77, 78). This evidence leads to the belief that dementia, and specifically AD, is a multi-causal disease with certain genetic factors partially determining how other neurological insults will manifest their damage in the brain.

The increased risk with E4 appears to be due to the fact that it accelerates the age of onset (48). In AD, the risk is increased with E4 in a dose-dependent manner (48). That is, the risk of AD increases, and the age at onset decreases, with the number of E4 alleles (72, 79). Compared to people with no copies of E4, the risk of developing AD in a person with two E4 copies is from eight to thirty times greater (80, 81), while those with one E4 allele have an increased risk of about three times greater (80, 82). In contrast, the E2 allele appears to be protective for the disease and is associated with a later age of onset if AD does develop (26, 80, 82, 83)

Evidence substantiates the biological importance of ApoE in neurological functioning. ApoE is present in the senile plaques of AD brains even in the early stages of formation (84) suggesting that ApoE accumulation precedes ß-amyloid deposition

(85). In contrast to the E4 genotype, the E2 and E3 alleles have different binding properties and may help to protect against the formation of amyloid aggregates, therefore hindering the development of senile plaques (86). The E4 allele is less able to limit the growth of the prerequisite plaque deposits in AD. ApoE also has an effect on tau protein. It is thought that E4 has a decreased binding to tau protein, which facilities neurofibrillary tangles leading to eventual neuronal loss (50).

Aside from AD, the development of other dementias and CIND (87), have been linked to ApoE-4 as well. ApoE-4 appears to increase risk of progression from mild cognitive impairments to dementia **(reference).** ApoE gentoype may also contribute to the neuropathological process in Lewy Body Disease (88), however it has not yet been found to influence the growth of AD lesions in Parkinson's disease (89). The frequency of ApoE-4 is increased in patients with vascular disease (48).

ApoE-4 does not predict AD with certainty. ApoE does seem to play a role in amyloid deposition and tau phosphorylation, but it is probable that it's only one of many factors (90). Although when AD is suspected and a clinical workup finds an ApoE-4 allele, the ApoE genotype has a positive predictive value of 94-98% (91). ApoE is a risk factor for the development of AD, but it is not necessary or sufficient to cause this illness (48). Rather than acting as a causative mechanism it seems to modify disease expression (50). Scientists continue to search for other contributory genes.

2.6 The Potential Interaction between ApoE and HRT

It is thought that HRT interacts with ApoE, thereby modifying its effects on the process of AD development. Studies have shown plasma levels of ApoE to be inversely correlated to the estrogen concentration in blood (92, 93). HRT may actually suppress APOE levels in women with low serum estrogen levels (59, 94). Furthermore, estrogen receptors have been shown to interact with the ApoE-4 genotype in determining onset susceptibility (91).

The mediation of ApoE-4's effects may be a crucial component of HRT's neuroprotective effect. Some of the benefits of estrogen may be related to the regeneration of the injured brain brought on by the neurotrophic action of ApoE itself (73). If this is the case, then HRT may be particularly important for postmenopausal women carrying E4 alleles.

2.7 HRT and Risk Reduction for Dementia

Considering estrogens putative neurological impact, it is a plausible hypothesis that HRT may preserve cognition function in aging women. Studies have shown that HRT may delay or prevent the development of dementia in postmenopausal women. It has been suggested that the risk of developing AD is reduced by 30 to 40% in estrogen users (95) with the severity of the disease also being reduced (96),(97). A meta-analysis of 10 observational studies, both retrospective case-controlled and prospective cohort studies, found that estrogen users had a 29% lower risk of developing AD (94). Still, research results are conflicting, with some studies finding no association.

Costa et al. (1999) found that postmenopausal women using estrogen have lower rates of possible and probable Alzheimer's disease (AD), than never users, and significantly higher rates of the lesser diagnoses of cognitive impairment and no dementia (98). Similar research, in both case-control and cohort studies, confirms that HRT users are at a decreased risk for developing AD as compared to non-users (96, 97, 99, 100-102). Most of the literature reviewed examines the development of AD specifically and not other forms of dementias. Of the ten studies found (See table 1), six show a clear protective association between HRT and AD. While two studies found no significant association (103, 104), both had smaller sample sizes, failed to assess duration of hormone use, and one relied solely on a prescription database as a marker of HRT use and compliance. Yet another study observed a protective association, but only after HRT was used for seven or more years (105). And recently, the WHI-MS observed an increased risk for dementia associated with HRT treatment (47). However, this effect was found in women beginning HRT at ages 65 and older, and therefore the disease process may have already been well underway. While some studies show support for a protective association, other studies have shown HRT to have no significant effects on cognitive functioning or the development of dementia. Therefore, further research needs to be conducted in order to discern the relationship between HRT and risk reduction for AD and other dementias.

Table 2.1: Literature Examining HRT as a Risk Factor for Alzheimer's disease and Dementia

First Author Year	Sample (n)	Study Design	Participants With Dementia	Sample age & education	Significant Findings OR (95%CI)	Covariates	Diagnostic criteria/ evaluation	Duration/ type/ dose of HRT	Comments on Methods
Shumaker, 2003 (47)	N=4894	Randomized, placebo-controlled, double-blind, clinical trial. Women's Health Initiative Memory Study.	61 cases probable dementia (32 AD cases) before non-adherence. 34 cases occurred after non-adherence.	65 years & older. Dementia-free @ baseline.	HRT-treated women were at twice the risk of general dementia (HR=2.05; 95% CI, 1.21-3.48). Risk was still significant when excluding non-adherent participants.	Did not differ according to age, education, smoking, diabetes, presence/absence of past hormone use, regular aspirin use, 3MSE scores @ baseline.	Screening interview, neuro battery, and annual clinical.	Conjugated equine estrogen & medroxy-progesterone acetate (combination therapy).	-Treatment @ 65 & older -Grouped AD & VaD together -HRT group (45%) & placebo group (47%) had used hormones prior to the study. Duration not assessed. -Blinding difficult -52% of women were non-adherent during the trial. More common in treatment group. -No APOE info -Many cases diagnosed after stopping HRT.
Geerlings, 2001 (106)	N=3601	Rotterdam Study. Pop-based, prospective cohort study. Median FU: 6.3 yrs	199 Incident cases of dementia (159 AD)	Ages 55 and over. Mean age @ baseline= 71.7 years. Dementia-free at baseline.	Women w/ longer reproductive period w/ APOE4 had an increased risk for dementia (RR=4.2; 1.97-8.92) and AD (RR=3.42; 1.51-7.75). In non-APOE4 carriers, no clear assoc.	Age, education, smoking and alcohol use, BMI, use of HRT, # of children, and APOE genotype.	Screening interview, neuro, clinical, and blood sampling.	HRT use was included as a confounder. 10% of sample were HRT ever users.	-Looked at both AD & general dementia. -More comprehensive list of covariates.
Seshandri, 2001(104)	N=280	Nested case-control in a cohort study. Population-based. Age-matched (within 5 years).	59 incident AD cases	Mean age= 66.7 (cases) & 65.2 (controls) Used General Practice Research Database.	Current vs. never: 1.18 (0.59-2.37) Current and past vs. never: 1.19 (0.62-2.27). BMI was found to be an independent risk factor for AD.	Body Mass Index, smoking, hypercholesterol-emia, diabetes mellitus, and ischemic heart disease.	Neuro assessment, clinical information obtained through physicians' notes; final Dx made by study neurologists.	# of prescriptions filled. Current, past, and never. 22% of cases & 21% of controls used HRT.	-Very few past users. -mean sample age=66 -Used records, participants were not seen. -no adjustment for other risk factors

Waring, 1999 (102)	N=444	Case-control study, population based. Matched by age and length enrolled in record linkage system.	222 AD cases.	All postmenopausal women. Median Education: 12.0 yrs.	0.42 (0.18-0.96) p=0.04 Longer use significantly decreased risk for AD.	Education, age @ menopause, and parity	Less standard; based on medical records. Diagnostic tests differed for each participant – not all had neuro tests.	Dose and duration.	-many women had other conditions. -used medical records linkage system. -Excluded ERT use < 6 months
Baldereschi 1998 (99)	N=1568	Cross-sectional population-based, multi-centre survey in Italy.	92 AD patients	65-84 years of age. Mean education: 5.1 (HRT never users) 6.1 (HRT ever users)	0.28 (0.08-0.98) *No difference in age of onset for AD.	Age, education, age @ menarche, smoking, alcohol habits, body weight @ age 50 & # of children.	Screened using MMSE, risk factor interview, neuro assessment, and clinical exam.	-Never vs. ever -Mean duration = 3 years -11.6% used ERT after menopause	Excluded non-AD dementia cases *Retrospective *ERT users younger, more educated, and drank more wine.
Kawas, 1997 (101)	N=514	16-year prospective cohort study.	34 incident cases of AD.	Mean age @ baseline= 61.5 years (28-94); 87% graduated college or greater	OR: 0.46 (0.209- 0.997) *No sig. effect of duration found.	Age, age at menopause, education, surgical menopause, and NSAID use.	Interview, clinical exam and neuro assessment. Reassessed every 2 years	Ever versus never users. 45% ERT users.	
Paganini-Hill, 1996 (97)	N=1488	Case-control nested within a prospective cohort. Leisure World Laguana Hills. Subset of those dying between 1981 and 1995. Age & death matched	248 AD cases. Dx taken from death certificates.	Mean age @ death: 87.7 (cases) 87.3 (controls)	OR for AD: 0.65 (0.49-0.88) Risk decreased with increasing dosages and duration of therapy (p=.01). Risk decreased for certain preparations.	Age @ menarche, weight, type of menopause, age @ last menstrual period, and BP meds.	Retrieved death certificate information for those dying b/t 1981-95. Participants did a health survey in 1981. Non-standardized diagnostic criteria.	Duration & dosage. Premarin most common. 96 cases used ERT & 578 controls used ERT.	--Time of dementia onset unknown. -Participant & proxy gave ERT info. -no clinical / neuro. -Age of onset of dementia not known. -No control for other risk factors.
Tang, 1996 (96)	N=1124 (all without dementia @ baseline) 36% Black 38% Hispanic 26% Caucasian	Cohort Study Assessed annually up to 5 years.	167 Incident AD cases.	Mean age 74.2 ; Mean education 9.2 years	***Overall:*** Adjusted RR for AD=0.40 (0.22-0.85) **ERT > 1 year:** RR for AD = 0.13 (0.02-0.92) Age of onset was sig. later for users than for never users. RR= 0.13 (0.02-0.95) for APOE4 hetero-zygous ERT users.	Education, APOE genotype, ethnic origin, and age.	Screen, Neuro assessment, clinical exam, and blood sampling.	156 ERT users (12%); Premarin was the most common. Ever vs. never Average duration of use = 6.8 years.	

Brenner, 1994 (103)	N=227	Pop-based, nested case-control, cohort study. Age-and sex-matched. Includes women with hysterectomy.	107 AD cases	Mean age=78.7 (cases) & 76.6 (controls)	OR: 1.1 (0.6- 1.8) No significant findings.	Education marital status, ethnicity, history of smoking and progesterone.	Medication history, MMSE, neuro assessment, clinical exam, lab tests, and imaging.	Current, past, and never users. Number of prescriptions filled. No duration or dose. Computerized pharmacy data confirms HRT use	Unknown if women actually took ERT. 61% of controls completed Grade 12, while only 12% of cases did.
Henderson, 1994 (100)	N=235	Retrospective case-control study. Volunteer community sample.	143 Probable AD cases	Mean age 76.0; Mean education 12.2 (cases) and 13.9 (controls)	AD patients were less likely to use ERT than controls (7% vs. 18%). AD patients using ERT did sig. better on MMSE than non-users.	Age, education, dementia symptom duration.	Interview, clinical exam, neuro assessment, and lab tests. Autopsy confirmed 70 of the AD patients.	Premarin was the most common ERT. Dose or duration not known.	*Volunteer sample *Retrospective *Only assessing current use. * Past ERT status not known.
Paganini-Hill, 1994 (105)	N=790	Case-control study nested within a prospective cohort study. Leisure World. Age & death date matched	138 AD cases	Mean age = 86.5 (cases) & 86.8 (controls)	Risk of AD for ERT users: 0.69 (0.46-1.03); ERT >=7 years OR= 0.49 (0.27-0.88) ; Dose>=1.25 OR = 0.46 (0.22-0.94). All other findings were not sig.	Age @ menarche ERT usage, type of meno-pause, age@ last menstrual period, BP meds, and stroke.	Mailed survey. Follow-up survey and hospital records. Pulled death certificates for those who died b/t 1981 & 1992.	Risk decreased with dose & increasing duration. Premarin most common.	No control for education, head injuries, NSAIDS use (other known risk factors).

2.8 HRT as a Treatment for AD

In addition to being a protective agent, HRT has also been studied as a potential treatment for AD. In the literature reviewed (see table 2), three studies found HRT to improve AD symptoms and three found no significant change in patients receiving treatment. Honjo et al. (1989) documented that ERT was associated with improvement in memory, orientation and calculation in patients with dementia (107). A study by Ohkura (1994) also provides evidence that dementia symptoms improve with ERT use (108). In a volunteer cohort study, Henderson, Watt, & Buckwalter (1996) selected three types of AD patients -- female HRT users, female HRT non-users, and men (109). They found that female AD patients using HRT scored better on the Boston Naming, digit spans forward and backward, and one drawing tests compared to female non-users. No differences were observed between HRT users and male patients. Conversely, in the Alzheimer's Disease Cooperative Study (ADCS), women who had had a hysterectomy and who had mild- to moderate- dementia were treated with ERT and no effect was found (110). If HRT is found to be an effective treatment for dementia, this would provide encouraging evidence for HRT's neuroprotective mechanism of action.

Currently, the only drugs approved to treat the cognitive dysfunction in AD are acetylcholinesterase inhibitors (57), such as donepezil and rivastigmine. However, this type of treatment can compensate for only part of the neuronal dysfunction in AD, and may not modify the oxidative damage or vascular dysfunction contributing to this illness (57). Estrogen has been shown to increase acetylcholine levels by enhancing the uptake of choline and activity of choline acetyl transferase in the hippocampus and frontal cortex (54), and therefore may provide benefits similar to current drug therapies. In addition, HRT may improve the effectiveness of current AD drug treatments. Estrogen appears to interact with tacrine suggesting that the choline acetyltransferase inhibitors require estrogen for their effects on cognitive function (111). Although clinical trials using HRT as a treatment for AD have not provided compelling evidence of effectiveness, they also cannot establish whether HRT is protective for AD when used prior to disease onset.

Table 2.2: Literature Examining HRT as a Treatment for Alzheimer's Disease

First Author year	Sample size	Study design	Sample characteristics	Significant effects OR (95% CI)	Covariates	Diagnostic criteria/ evaluation	Duration/ type/ dose of HRT	Comments on methodology
Henderson (112) 2000	N=42 (21 placebo & 21 ERT)	Randomized, double blind, placebo-controlled, parallel-group trial.	All mild to moderate AD. Mean age: 78 (placebo) 77 (ERT treated group) Education: 71% (placebo) and 81% (ERT treated group) completed grade 12	No sig. differences found.	At baseline the treatment & placebo groups did not differ acc. to characteristics.	ADAS-Cog; CGIC; ADL/IADL. Mood assessed. Neuropsych test battery.	Treatment: Premarin 1.25mg/ day for 6 weeks.	-80% power. -Difficult to blind women b/c of bleeding. -Short treatment duration.
Mulnard 2000 (110)	N=120	Randomized double-blind, placebo-controlled, clinical trial b/t 1995-99. Assessed @ baseline, 2, 6, 12, & 15 months.	All mild to moderate AD. *All had a hysterectomy *Mean age = 75 *Mean education = 12 yrs	No significant improvements in ERT-treated group.	Age, APOE4 allelle frequency, and education.	CGIC (Clinical Global Impression of Change) ADL's, and other neuro tests.	0.625 mg/ day of Estrogen (n=42); 1.25 mg/ day of Estrogen (n=39); Placebo (n=39) treatment: 12 months of premarin.	-Assessed intent-to-treat. -30% of placebo group were past ERT users
Wang (69) 2000	N=50 (25 placebo & 25 treatment group)	Randomized double-blind, placebo-controlled 12-week trial.	All mild to moderate AD patients. 60 yrs and older. Mean age = 72.6 (ERT treated group) 71.0 (placebo) Mean education = 6.9 (ERT treated group) 4.9 (placebo)	No sig. differences found b/t treatment and placebo group.	No sig. differences b/t treatment groups.	CASI, CDR, CIBIC-plus. BEHAVE-AD: HARS, HDRS. Cerebral blood flow. Blood tests used to assess compliance.	Premarin 1.25mg/day vs. placebo. *all patients were not taking any other anti-dementia meds during this 12-week period.	80% of power -quite a healthy sample.
Asthana (113) 1999	N=12	Placebo-controlled double-blind, parallel-group design pilot clinical study.	All participants had mild-to-moderate AD. Mean age of ERT users = 79.5; of placebo = 77.6. Mean education of ERT users = 11.3; of placebo = 13	Sig. effects of ERT on attention ($p<0.03$) & verbal memory ($p<0.02$). *Effects decreased after stopping treatment.	Not specified	Evaluated @ baseline, 1, 3, 5, and 8 weeks. And at 9, 10, 11, and 13 weeks off treatment. *Neuro tests *Blood samples to measure estrogen in blood	8-week ERT (estradiol) to 6 participants via skin patch and 6 participants received placebo via skin patch.	Several markers of neuroendocrine activity may serve to index the magnitude of estrogen-induced facilitation on cognition. All participants free of depressive symptoms

Schneider (114) 1997	N=323	30-week randomized, double-blind, placebo-controlled, multicentre clinical trial	All with dementia. 50 yrs and older.	Women receiving HRT & tacrine improved sig. more than women not receiving HRT & who were randomized to placebo or tacrine as assessed by caregiver ($p = 0.006$) and clinical ($p = 0.02$).	Not specified.	AD Assessment Scale-Cog. Scale (ADASc) & clinician's interview based impression of change (CIBI) & caregiver's impression of changed (CIC).	-14.5% of women were currently using HRT) -Treatment: Placebo & one of three doses of tacrine. -HRT was not administered. Only assessed for current users. Most common was Premarin (86%) and estradiol (12%).	Tacrine was the only treatment randomized (not HRT). Duration and dose of HRT not known. HRT users were younger (67 years +-9 vs. 74 years +- 8), and more non-HRT users did not complete high schools (16% vs. 4%). -did not control for age, education, or duration of HRT use b/c of randomization, which didn't create totally equal groups.
Henderson (109) 1996	N=62	Case-control study. Drawn from volunteer cohort study. Matched for age, education, and age dementia symptoms first appeared.	All AD patients. Selected 9 women using ERT & 27 women not using ERT & 26 men. Mean age=74.7 (ERT users) & 74.3 (ERT non-users) Mean education: 12.7 (ERT users) &13.3 (ERT non-users)	Women with AD using ERT scored better than non-ERT using women on Boston Naming , digit spans forward & backward, & 1 of the drawing tasks. No sig. differences between ERT-treated group & men.	Matched on age, education, and age symptoms first appeared.	Screen, neuro, clinical, CT & MRI scans of the brain.	Premarin most common.	Of the ERT non-users: 12 had no known use of ERT, 6 used ERT in the past, and 9 participants did not know.

2.9 HRT and Cognition in Women Without Dementia

Studies have examined HRT's effects on cognition by using younger, female populations without dementia (See Table 3). Research in this area has generally shown better test performance for HRT users, both past and present, over never users (65, 115-123). Two studies found no significant differences in cognitive ability (18, 124), while one study's only significant protective effect was seen in women with surgically-induced menopause (125). Any improvement in test performance induced by HRT, even in a younger sample, may lend support for HRT as a protective factor in cognition. Similar to other research in this area, there are methodological limitations in this line of research. Lack of test standardization, clinical evaluation, small sample sizes, and limited control for confounders are some such biases.

Table 2.3: Literature Examining HRT as a Risk Factor for Cognitive Decline

First Author Year	Sample (n)	Study design	Sample characteristics	Significant findings	Covariates	Cognitive tests	Duration/ type/dose of HRT	Comments on methodology
Rapp, S. (126), 2003	N=4381	Randomized, placebo-controlled, double-blind, clinical trial. Women's Health Initiative Memory Study.	65 years & older. Dementia-free @ baseline.	HRT did not improve global cognitive function when compared to placebo. More womem n the HRT group as compared to the placebo (6.7% vs. 4.8%) declined by 2 SDs on the 3MSE.	Did not differ according to age, education, smoking, diabetes, presence/absence of past hormone use, regular aspirin use, 3MSE scores @ baseline.	Screening interview, neuro battery, and annual clinical. Main outcome measure was global cognitive function	Conjugated equine estrogen & medroxy-progesterone acetate (combination therapy).	- assessed effect of prior use and duration of prior use.
Shumaker, S. (47), 2003	N=4894 (including dementia cases)	Randomized, placebo-controlled, double-blind, clinical trial. Women's Health Initiative Memory Study.	65 years & older. Dementia-free @ baseline.	HRT had no treatment effect on Mild Cognitive Impairment (MCI).	Did not differ according to age, education, smoking, diabetes, presence/absence of past hormone use, regular aspirin use, 3MSE scores @ baseline.	Screening interview, neuro battery, and annual clinical.	Conjugated equine estrogen & medroxy-progesterone acetate (combination therapy).	-removed prevalent MCI & dementia cases -151 MCI cases in total
Carlson, MC. (127), 2001	N=2073	Community-dwelling females anges 65 & older		Age, lower education, depression, and APOE were all associated with lower baseline 3MS scores. Lifetime HRT use was associated with improved global cognition & attenuated decline over a 3-yr interval. Improvements greatest in the oldest old.	Multivitamins, calcium supplements, APOE-4, age, education, concurrent depression, chronic disease, self-perceived general health.	Modified MMSE, phone interview, clinical assessment.	Current and past HRT meds @ baseline & 3 year later recorded.	-Dementia cases removed from model.
Fillenbaum (124) 2001	N=1907	Cohort study. Stratified random sample. Black and white women Ages 65-100	Mean age = 72.8 (64-100); Mean education = 9.5 yrs All cognitively normal.	Crude OR: 0.42 (0.21-0.86) and 0.32 (0.13-0.81) No significant findings after adjusting for confounders.	Age, sex, education, race, marital status, smoking, drinking, NSAIDS, and health behaviours, conditions, and self-rated health status.	Screen: SPMSQ Evaluated @ baseline, 3 and 6 years.	Cross-checked ERT use with records. Recent, past, continuous, and intermittent use of ERT assessed. Dose & duration used.	After adjustment effects were non-significant. Only a screen used to determine cognitive impairment and decline. No clinical exam. Deceased participants not used in analysis.

Duka (118) 2000	N=37	Randomized, double-blind, placebo-controlled clinical trial.	Ages 55 to 75 yrs (mean 65)	Memory function & spatial abilities sig. improved with ERT independently of mood or general well-being.	N/A	Psychometric test battery & verbal IQ test. POMS	ERT for 3 weeks (n=19) or placebo (n=18) Estrogen plasma levels tested.	Only 1 participant has previously used ERT. Very healthy sample (eg. BMI 15% of normal nonsmokers)
Rice (116) 2000	N=837	Cohort Study. FU: 2 yrs.	Postmenopausal Japanese-American women. 65 and older.	Modest increase in cognition in ERT users vs. never users.	Age, education, language, surgical menopause, and baseline CASI score.	CASI	455 never users 186 past users, 132 current estrogen users, 64 current HRT users	-only one test of cognition. -no clinical evaluation
Shaywitz (128) 2000	N=46	Randomized, double-blind, placebo-controlled, crossover trial Volunteer sample	No dementia; all healthy postmenopausal women Ages 33-61 (mean 50.8)	No effects of ERT on performance of verbal & nonverbal tasks. Changes in brain activation patterns.	None mentioned.	Brain activation patterns measured using imaging during verbal & nonverbal tasks.	No hormones for at least 3 months prior to study. 2 periods of 21-days of ERT and placebo.	participants had normal MRI findings, an IQ of at least 85, in good health, and had a menstrual period at least 5 months prior to entry. Past ERT use unknown.
Matthews (120) 1999	N=9651	Prospective cohort study FU @ 2 & 6 yrs.	65 & older Mean age = 71.7; mean education=12.6 yrs	Current & past users of ERT had sig. better scores on 3MS than never users, with better scores for current users most apparent in older & less educated women.	Age, education, activity limitations, stroke, and depression scores.	MMMSE, digit symbol substitution, & Trails B test.	Past, current, and never use of ERT. 79% of hormone users used ERT. Avg. duration for current users (14.3 yrs); past (5.2 yrs)	Estrogen users were younger, better educated, more likely to be nonsmokers and less obese than never users. No difference b/t self-reported health status of groups.
Steffens (117) 1999	N=2338	Cross-sectional study.	Healthy women (in a Mormon community). Excludes patients with stroke or dementia, as well as those with 3MSE scores under 65. 65 & older. Mean age = 75.1	After adjustment, HRT never use, current depression, poorer perceived health status, and APOE-4 allele(s) predicted poorer 3MSE scores. -Current & past ERT 3MSE scores > than never-users.	Education, Age, health status, APOE, depression, & history of head injury.	Modified Mini-Mental State Examination (3MSE) *clinical and neuro assessments were used to exclude participants with dementia.	Never, current, & past users. Duration assessed.	-Very healthy sample. -Type of HRT not asked.

Jacobs (119) 1998	N=727	Community-based longitudinal study. FU: 2.5 yrs	Mean age = 74.2 Mean education = 9.4 yrs White, African-American & Hispanic	ERT users scored sig. higher on tests @ baseline than nonusers & ERT users improved slightly over time. Effects of ERT indep. of APOE status.	Age, education, ethnicity, and APOE genotype.	Clinical and neuro test battery. Selective Reminding test, WAIS-R Similarities, Boston Naming, and delayed recall on Selective Reminding test.	11% ever users. Avg. duration of ERT use = 4.5 yrs. Only 2% were current users.	Current ERT users were sig. younger & better educated others. When removed from analysis there was no change. Excluded all dementia sufferers
Resnick (122) 1997	N=288	Prospective cohort study Baltimore Longitudinal Study of Aging	All postmenopausal women	ERT users had fewer errors on the BVRT. ERT seemed to protect against age changes in BVRT performance in a subset 18.	Not specified.	Benton Visual Retention Test.	116 ERT current users 172 never users	Duration not assessed.
Szklo (125) 1996	N=6110	Longitudinal study; FU: 3 yrs. ARIC study.	No dementia. Ages 48-67; both African-American and white.	Only affect seen in surgically menopausal women. No consistent effects.	Age, education, race, marital status, self-reported health status, depression score, smoking, drinking, hypertension, diabetes, plasma fibrinogen, BMI, sport index, & time fr menopause for PM women.	Delayed Word Recall, Digit Symbol Subtest of the Weschler Adult Intelligence Scale-Revised, and the Word Fluency test of the Multilingual Aphasia Exam.	Current vs. never users Duration assessed.	-No clinical examination. -only 3 cognitive tests used. -sample selection not given.
Fielding (115) 1992	N=18	Clinical trial 8 estrogen deficient &10 pre-menopausal women.	No dementia; all healthy women Ages 35-64	Estrogen deficient women improved in all areas, with sig. increase in emotional status.	Not known	13 brief neuro tests @ baseline. Retested after 2 months of treatment.	ERT administered for 2 months to estrogen deficient group.	-Estrogen-deficient women's profile differed from estrogen normal participants. -no clinical -short-term ERT duration.
Phillips (65) 1992	N=19	Randomized, double-blind, placebo-controlled, clinical trial	Women with a hysterectomy & oophorectomy for benign disease	Scores on the immediate & delayed recall of paired-associates unchanged for ERT group, but placebo declined. Immediate recall of paragraphs improved in ERT group, no change in placebo.	N/A	Weschler Memory Scale, Menopausal Index, & Multiple Affect Adjective Check List.	Injected ERT (n=10) & placebo (n=10). 2 months. Blood test for estrogen levels.	All participants had never used HRT prior to trial.

2.10 Methodological Issues in Current Research on HRT and Cognition

There have been important methodological limitations in previous studies that explore the relationship between HRT and cognition. In particular, differences in neuropsychological test batteries, research designs, duration of treatment, type of hormone used or administered, age of participants, sample size, sample selection, proxy and participant recall of past hormone use, differing adjustments for confounders and effect modification in analyses are examples of discrepancies between studies. Together these variations in the research process may have a significant impact on the nature and strength of any association found.

Known risk factors for dementia and AD are age, educational attainment, APOE-4 genotype, NSAID use, and past head injury (70). These important known dementia risk factors have not been taken into account in numerous studies examining HRT's effects, thereby potentially distorting findings. NSAID use and ApoE genotype have not been routinely controlled for in HRT analysis, with only a few studies assessing NSAID use (101, 122, 124) and ApoE status (96, 106). As well, the interaction between estrogen use and APOE-4 presence has been largely overlooked (94). Furthermore, age at menopause and type of menopause have not been consistently controlled for (100, 103, 104, 106, 124) (96), yet both may be a measure of length of estrogen deprivation and therefore highly relevant. Age and educational attainment are the standard risk factors included in analysis (99-101, 124) (96, 102, 103, 106). Even while controlling for the known risk factors, results have been inconsistent. After adjusting for covariates several study findings became no longer significant, therefore it is crucial that independent risk factors, confounders, and effect modifiers be taken into account when attempting to provide evidence for causation.

When relevant factors are identified they can be controlled for in analysis, however some other factors may be less evident. At present, the nature of the relationship between HRT and cognition has not been fully explored. The failure to measure significant factors such as differences in the health-seeking behaviour (129) or socioeconomic status (SES) of women using or not using estrogen(130) is an important limitation to current research. As will be discussed in the following section, differences between users and non-users of HRT may exist and may confound the HRT-cognition

relationship. If explored, these factors may help to clarify the association between HRT and cognition, thereby explaining the myriad of findings to date. To resolve important unanswered clinical issues, new information from basic research and from large randomized treatment studies, cohort studies, and case-control studies is needed (19).

Each study design, whether it is cross-sectional, case-control, cohort, or a clinical trial, has the potential for bias. In general, case-control and cross-sectional studies experience more biases stemming from their research design (131). As they are done only at one point in time, cross-sectional studies are not able to trace the progression of a disease and lend little support for cause-and-effect relationships. Likely because of their shorter duration and cost, case-control studies have been more commonly used to investigate HRT's association to cognitive decline and dementia. Limitations of case-control studies include: methods of case ascertainment, selection and matching of controls, methods of obtaining ERT information (participant, proxy, medical records), and exposure of interest (current use versus lifetime use). Controls may also have CIND or be in pre-clinical phases of dementia. Due to their retrospective nature, recall bias is a concern, especially by participants with dementia and by proxies unaware of ERT use decades earlier. Prospective cohort studies are less likely to be affected by these biases. Using a cohort design allows the investigator(s) to follow participants over time (sometimes decades), while prospectively gathering exposure information at regular intervals.

The multitude of findings in studies reported in the literature can be puzzling, however differences in research designs may offer a partial explanation. Particularly, in observational studies where the form of HRT cannot be manipulated, different types of HRT preparations may have disparate affects. In one study, estrogen and progesterone combined were found to be neuroprotective, however medroxyprogesterone acetate (MPA), a different type of progesterone, failed to do the same, but instead decreased the estrogen-induced neuroprotection when co-administered (132). Furthermore, there may be differences in the estrogen response between women. Age-related physiological changes, such as body composition, nutritional status, plasma proteins, and their estrogen-binding capacity, and metabolic changes due to liver and kidney malfunction may affect the clinical response to estrogen (57).

As a means of avoiding biases inherent in the observational studies, clinical trials are often deemed the "gold standard" in epidemiology. However, caution must be used in interpreting the results from experimental studies. If HRT is a useful preventative factor for dementia, randomized, placebo-controlled, clinical trials may not be able to detect long-term effects because of their usual shorter duration. In clinical trials, women not using HRT therapy may have been estrogen deprived for many years, and this produces irreversible changes in the structure and function of estrogen target neurons in the brain and their sensitivity to estrogen (57). It would follow that the estrogen-responsive neuronal and vascular elements may not be responsive to estrogen administration (57). Moreover, blinding women in double blind, placebo-controlled trials is difficult, if not impossible, due to frequent breakthrough bleeding and other notable side-effects of HRT therapy.

2.11 Prevention Bias

An important question that needs to be answered when studying the effects of HRT is -- "do HRT users differ from non-users?" (129). That is, prior to starting HRT, do the personal characteristics, lifestyle choices, health behaviours, and health status of users confer some protection over and above that of non-users? This issue needs to be considered before any beneficial effect can be attributed to HRT, especially in observational studies where participants are not randomized to treatments. Even in clinical trials, researchers must control for differences that are not eliminated through randomization. If there are pre-existing differences between HRT-users and non-users that are not controlled for in analysis, such as SES, education, and health-seeking behaviour (129), then the protective effects of these characteristics may be erroneously attributed to HRT use.

There are two significant biases that may skew study findings when examining HRT's relationship to dementia. First, do HRT-users differ characteristically from women not using HRT? Finley, Gregg, Soloman, and Gay (2001) in a study on the socio-demographic, psychological, and behavioural correlates of HRT use, found that higher income, hysterectomy, younger age, regular adherence to cervical screening, and physician encouragement of hormone therapy were all significantly associated with its

use (133). In addition, Barret-Connor (1991) observed that HRT-users in an upper-middle class cohort exhibited healthier behaviours such as more reported exercise, weight loss, stress reduction, increased dietary fiber, potassium, and calcium than non-users (129). Even within socioeconomically homogenous groups, differences can exist between users and non-users with regard to health promotion and disease prevention measures (129). In another study, HRT-users were more likely than non-users to get a mammogram, stool test, cholesterol check, and Pap smear (129, 134), however these factors would likely influence coronary heart disease and cancer more than dementia (129). In a national population-based cohort study, HRT use was almost four times more common among college graduates than those not graduating from high school, in non-smokers, women with a lower body mass index, and less common among diabetics (135). In the Canadian National Population Heath Survey (NPHS), women using HRT were found to have more frequent contact with their family physician, as well as to have had a mammogram, blood pressure check, and to be currently using anti-depressants (26). However, doctor visits are often used to refill prescriptions and physicians often recommend screening tests to HRT users (31). Many of these factors associated with HRT use could potentially confound the HRT-dementia relationship and need to be accounted for in data analysis.

Another important bias associated with HRT use is survival bias. Because dementia studies rely on older, female participants, any effect of HRT on longevity is important. One study found that estrogen use was associated with a 46% lower age-adjusted risk of mortality, with longer durations of use being more protective than shorter periods of estrogen treatment (136). Reduction in mortality from CHD and cardiovascular disease accounted for most of this increased survival (136), a finding that may impact the survival of women who may be potentially at risk for developing vascular dementia and AD. Survival bias is not easily assessed in studies that include women of advanced age at baseline. Still studies of HRT must consider the extent to which these biases can explain some or all of the observed differences (129).

2.12 Other Risk Factors For Dementia

At present, epidemiological research has identified several risk factors that may contribute to, or protect from, dementia. Taken together these factors may help to

determine the likelihood of an individual developing this illness. Because the presence of each exposure may increase or decrease one's risk profile, it is imperative that these factors be statistically controlled for in analyses. Each of the following is thought to be an independent risk factor for the development of dementia, although studies findings for each variable may conflict. These covariates may also act as effect modifiers in the relationship between HRT use and susceptibility to dementia.

Age

Changes in cognitive abilities may be natural as people age, however the degree of change, and the process responsible for this change, is quite different in dementia as compared to normal aging. The risk of AD increases by 23% each year after 65 (137). A direct relationship between age and incidence of dementia has been consistently observed, thereby making age a definite risk factor.

Education

In the CSHA, participants with 0-6 years, 7-9 years, or 10 or more years of education had odds ratios of 4.0, 1.72 and 1.00, respectively (70). The exact relationship of education to dementia has not yet been determined, because low education may be a surrogate marker for other risk factors or may bias neuropsychological test results. The "brain reserve hypothesis" postulates that greater educational attainment increases brain reserve by increasing synaptic density, therefore delaying AD's clinical onset by 4 to 5 years in more educated individuals (138). Although study results differ, low or no education seems to put one at the greatest risk.

NSAID Use & Arthritis

In theory, an important component of the AD process is inflammation in the brain. Studies have revealed that anti-inflammatory agents like NSAIDs are associated with a decreased risk of AD, especially with prolonged use (139). In CSHA, an OR of 0.65 was found with NSAID use (137). NSAIDs, such as ibuprofen, are often used to relieve the pain associated with arthritis – a condition common in seniors – that has also been found to be independently associated with decreased risk of AD (137).

Past History of Head Injury

Using the combined data from 11 case-control studies, the European Action Group on the Epidemiology and Prevention of Dementia (EURODEM) Risk Factors

Research Group found that participants with a history of head trauma with loss of consciousness had a Relative Risk (RR) of 1.82 (1.26-2.67) (140). This finding was independent of family history of dementia, education, and alcohol consumption. As previously described, exposure to head injury and ApoE-4 presence have been found to interact as well.

Regular Physical Activity

A physically active lifestyle can be protective for a variety of illnesses. In the CSHA, participants who had regular physical activity had a decreased risk for AD (OR=0.69; 95%CI 0.50-0.96) (137). This association was similar for cognitive impairment and other dementias, with a significant trend for increased protection with greater activity being observed (141).

Wine Consumption

Wine drinking has been found to improve vascular function and decrease risk for heart disease. In the CSHA, weekly consumption of wine appeared protective for AD (OR=0.49; 95%CI 0.28-0.88) (137).

Alcohol Consumption

Studies have found that not only wine drinking, but hard liquor consumption can have a beneficial effect on the development of dementia. In one particular study, moderate drinkers (one - three drinks/ day) showed a reduced risk for any dementia (hazard ratio 0.58 [95% CI 0.38-0.90]) and for vascular dementia (hazard ratio 0.29 [0.09-0.93]) than for nondrinkers – without any evidence to suggest that this relationship depended on the type of alcoholic beverage (142).

Coffee and Tea Drinking

Tea has been found to contain disease-fighting antioxidants known as catechins and flavonoids (143). These antioxidants may protect from the development of dementia. Recent analysis by McDowell (49) revealed that coffee drinking also may be a protective factor in the disease process. It is possible that caffeine is responsible for this beneficial effect, although other studies with similar findings are not known.

Smoking

In the CSHA, the mean age of onset of AD was significantly lower in smokers (80.07) than in nonsmokers (83.85). However, smoking was only a significant risk

factor for AD in heavy smokers (37+ pack-years) (OR=2.79; 1.27-6.14) (70). In terms of its relationship to HRT, moderate smoking results in less biologically available estradiol in women taking estrogens (20), therefore may interact with HRT's effects.

Occupational Exposures

Exposure to glues, pesticides, and fertilizers appear to be risk factors for AD, even after controlling for age, sex, and residence (70). In the CSHA,when stratifying by level of education, the risk remained elevated for the lower two levels (0-6yrs and 7-9 yrs), but not for the highest level (10 or more yrs). The association between fertilizers and pesticides was not significant after controlling for education.

Health Conditions

Vascular disease is known to contribute to the development of dementia. Heart attack, stroke, Parkinson's disease, diabetes, thyroid conditions, kidney disease, high blood pressure and arthritis will be included in this analysis to control for the effects of such chronic illness. Often in dementia-related research, these variables are not consistently accounted for.

Income

Although income has not been well-established as an independent risk factor for dementia, some evidence suggests that it may be a significant predictor of disease development (144). Level of income is often combined in a measure with education and occupation called socioeconomic status (SES). By using income in this analysis, factors related to economic disparities may be controlled for separately from the influence of education.

Statin Use

Epidemiological research suggests that statins, often used to treat hypertension, may significantly decrease one's risk for developing dementia (145). Recent clinical data indicates that statins may protect against disease by modifying the effects of APOE-4 (146).

Vitamin Use

Vitamin use has been linked to cognitive impairments (147). Antioxidants such as vitamin E and C have been studied more closely, while research is being carried out

looking at Vitamins B. High levels of the amino acid homocysteine have been found to increase Alzheimer's risk, which can be lowered by taking folic acid(148).

Head Injury

Research has linked head injury and dementia, although the findings have been inconsistent. In so much as head injuries can damage the brain, the impact of head trauma on disease development appears to interact with APOE status.

Marital Status

Marriage may benefit cognition in both men and women, in that the prevalence of dementia is lower in people who are currently married or who have been previously married than in those who have never married (149).

Depression

Meta-analysis has confirmed depression is related to dementia (150). The exact nature of the relationship is unclear. In a large prospective study, the hypothesis that older women without dementia but with depressive symptoms have worse cognitive function and greater cognitive decline than women with few or no symptoms was tested. It was found that cognitive change scores were directly correlated with the number of depressive symptoms ($P<.001$) (151). The results were similar after adjusting for education, age, health status, exercise, alcohol use, functional status, and clinic site. Evidence suggests that history of depression may not only diminish cognitive ability, but is also risk factor for dementia (150).

2.1 Overall Conclusion

The relationship between HRT status and cognition is not yet resolved. With many studies reporting positive results; some reporting no association; and the WHI-MS reporting a negative association, it is difficult to navigate through the research and be able to comfortably draw conclusions. Methodological problems in HRT studies such as study design, sample size, exposure ascertainment, and outcome assessment limit the reliability and validity of study conclusions. Similarly, biases such as prevention bias confound the association between HRT and cognition making interpretation of research results problematic. Finally, many new risk factors for cognitive decline and dementia are being explored and there are likely many unknown

risks associated with disease development. This emphasizes the importance of adequate control for group differences and suspected covariates.

2.2 Significance of Study

Understanding the relationship between HRT and cognitive decline is highly relevant to clinicians and women in general. Doctors and researchers need to know if HRT, in fact, does have a protective effect on cognition and if this effect is clinically significant. Identifying the cognitive advantages of HRT is an essential element of each woman's risk-benefit considerations. This thesis will add to literature by using a strong study design, controlling for relevant and unexplored risk factors, relying on incident cases, and including a thorough clinical examination used to determine cognitive status. It will also assess group difference between HRT users and never users, thereby examining any impact these variations may have on the study findings.

CHAPTER 3: METHODOLOGY

3.1 Study Design

In studying the relationship between cognitive impairments and HRT, the CSHA-1 and -2 datasets were used for all analyses. The CSHA is a population-based, prospective, cohort study with a nested case-control sub-study. It involves 18 study sites across Canada and is coordinated by the University of Ottawa. Of people 65 and older, 10,263 study participants were randomly selected from 36 communities across Canada and interviewed three times in 1991-92, in 1995-96, and again in 2001-02. At baseline, samples were drawn from both the community (n=9008) and institutions (n=1255). Participants are fluent in either English or French. The 1991-92 data collection provides baseline, prevalence, and risk factor data for cognitive impairments and dementias. The 1995-96 and 2001-2 data supply incidence, risk factor, and outcome data. For those individuals who died between study phases, the cause of death information was retrieved and a family member or close friend interviewed. The most recent data collection phase (CSHA-3) was unavailable at the time of thesis analysis and write-up.

A variety of different sources were used to obtain information regarding the participants' risk factor exposures and cognitive status. During CSHA-1, a risk factor questionnaire was completed inquiring about both current and past exposures and illness. If the participant scored above the cut-off (77/100) on the cognitive screening test, this information was obtained from the participant; if at or below the cut-off, then the closest family member or friend was asked to act as a proxy respondent. During all study phases, able participants met with interviewers to complete a general, in-person interview that deals with the respondent's physical, mental, and social health. The Modified Mini-mental State exam (3MS), a neuropsychological test sensitive to

impaired cognitive functioning, was used as a screening tool. Potential cases, both those exhibiting cognitive impairment (according to 3MS scores) and age, sex, and residence matched-controls, were asked to participate in further neuropsychological tests, a physical examination, and blood sampling. If the participants were unable to attend a screening interview, they were asked to go directly for clinical assessment.

3.2 Identification of Cases

Each potential case was discussed at a consensus conference, which included the study physician and neuropsychologist, to obtain a diagnosis. Prior to the consensus conference, both the study physician and neuropsychologist made a preliminary diagnosis based on their own assessments, the screening interview, and the informant questionnaire (physician only). During CSHA-2 and -3, final diagnoses also included the examination of previous neuropsychological test scores, 3MS scores, and activities of daily living (ADLs). Possible diagnoses include:

-no cognitive impairment (*without* CLoND)

-no cognitive impairment (*with* CLoND)

-Cognitive impairment no dementia (CIND) (*without* CLoND)

-Cognitive impairment no dementia (CIND) (*with* CLoND)

-Alzheimer's disease (possible or probable)

-Vascular dementia (acute onset, cortical, subcortical, mixed cortical / subcortical)

-other specific dementia (Parkinson's, Pick's, Huntington's, Creuztfeldt-Jacob, post-head injury and other)

-unclassifiable dementia

Severity of all diagnoses were rated using a three-point scale at time-one and Reisberg's Global Deterioration Scale(25) at time-two and -three. As well, the presence of co-existing disease and the contribution, or lack thereof, of such disease to the diagnosis of CIND or dementia was specified. For participants unable to complete screening or neuropsychological testing, the clinical assessment was the basis for diagnosis.

At time-one (CSHA-1) general dementia diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R)(152) and at time-two and -three diagnostic criteria followed DSM-IV(24).

Alzheimer's disease diagnoses followed the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)(153) criteria at time-one and DSM-IV at time-two and -three. The International Classification of Diseases, 10th revision (ICD-10) (154) criteria was used to diagnose vascular dementia at time-one and the National Institute of Neurological Disorders and Stroke criteria (NINDS-AIREN)(27) at time-two and -three. During CSHA-2 and-3 consensus conferences, two diagnoses were made using both of the criteria specified above. This was done in an effort to standardize each study wave. Data collection at each phase followed the same format – in addition to tracking deaths at CSHA-2 (1995-96) and CSHA-3 (2001-2). For the purposes of this thesis research work, the most current diagnostic criteria have been used to identify cases at each phase.

Table 3.1: Screening Cut-off and Diagnostic Criteria at Each Study Phase

	CSHA-1	**CSHA-2**	**CSHA-3**
Screening Interview cut-off	78	78	90
Severity of Diagnosis	Three Point Scale	Reisberg's Global Deterioration	Reisberg's Global Deterioration
Dementia Diagnosis	DSM-III-R	DSM-IV	DSM-IV
Alzheimer's Disease	NINCDS-ADRDA	DSM-IV	DSM-IV
Vascular Dementia	ICD-10	NINDS-AIREN	NINDS-AIREN

3.3 Study Sample

3.3.1 Inclusion and Exclusion Criteria

Initially, 6,255 women participated in the first phase of the CSHA. However, in order to be included in this particular analyses, female participants must have had available HRT information at time-2 and been dementia free at baseline. Since HRT information was only obtained during CSHA-2, this required that women who had died between CSHA-1 and -2 be excluded from the sample. After accounting for those participants with missing HRT information, lost to follow-up, deceased, or with dementia at CSHA-1, 3,384 women remained for analysis.

3.3.2 Sample Size and Statistical Power

The program Epi Info 2002 was used to calculate statistical power based on the study's sample size. Power calculations were completed for each outcome, since the incidence of each outcome differed. For AD, at a 4% incidence in the unexposed group (HRT never users), an estimate of power for this sample size with a maximum detectable effect of OR=0.50 is 80%. For CIND, at 11% incidence in the unexposed group, power estimates of 80% for an OR of 0.65 was expected. [See Table 3.2]. Finally for VaD, which has a 1% incidence in the unexposed group, 80% power was estimated for an effect no larger than OR=0.10. Although the overall sample is quite large, the sample sizes for each outcome are smaller as they include only one outcome (eg. CIND, AD, or VaD), and then the cognitively normal group. Consequently, the statistical power is quite low for VaD, and lower than expected for CIND and AD. Nonetheless, for the outcomes CIND and AD, the power of this study allows for the detection of moderate to large effects, which are more likely to be clinically significant at a 95% confidence interval.

Table 3.2: Power Estimate Calculations According to Incidence and Effect Size

	AD	**VaD**	**CIND**
Maximum Detectable Effect (OR)	0.50	0.10	0.65
Incidence (%)	4	1	11
Confidence Interval (%)	95	90	95
Power Estimate (%)	80	80	80

3.4 Variable Coding

3.4.1 Variable Selection

The decision of which specific variables to include in analysis was based on the literature, where evidence is mounting for a range of potentially relevant exposures. In this way, this study not only tests the importance of HRT as a predictor of cognitive decline and disease, but also it is to some extent a gender-based analysis examining the impact of many other indeterminate risks on women's cognition in general.

In addition to the risks identified in the literature, other general indicators of lifestyle and health status were also examined at the bivariate level, and if significant, were included in the multivariable analysis. These additional factors were included to assess and control for interaction and confounding. Although some potentially relevant information was not obtained during the course of the CSHA; and therefore, variables such as hysterectomy status, age at first and last menstrual period, and use of natural sources of phytoestrogens were not available for analysis. In addition, self-rated health status and Body Mass Index were only asked for a portion of the female sample and were also omitted from consideration as covariates. All of these factors could potentially impact the relationship between HRT and cognitive decline.

3.4.2 Risk Factor Information

The CSHA is a comprehensive study that aims to identify many of the potentially important risk factors for cognitive decline, and conversely, healthy aging. Data was collected on a variety of different lifestyle, environmental, social, familial risk factors along with data on different health conditions and diseases. These include both risk factors present at the time of interview and even some dating back to the participant's youth.

Risk factor information was obtained from several sources (i.e. screening and informant interview, clinical assessment, and risk factor questionnaire) throughout the CSHA. Notably, there was a good deal of missing variable information in the CSHA. Therefore it became necessary to combine data sources in order to create the necessary profile of risk for each individual. This is largely due to the study's nested case-control component, which was created specifically to examine risk and protective factors and the contribution of such factors to cognitive decline, impairment, and dementia development. The study was structured so that many of the risk factor variables were located in the informant and clinical interviews; hence, data were more complete for those who received a clinical examination. While comprehensive, this approach runs the risk of gathering sometimes conflicting information. The lack of consistency poses a dilemma for researchers trying to get a reliable history of risk factor exposure. However, the above method of combining variables from different sources will allow for more complete risk profile information for the entire sample.

At baseline, both participants and proxies were given risk factor questionnaires to fill out following a screening interview. If the participant screened above the cut-off, the participant was asked to complete the questionnaire. If the participant screened below the cut-off, a proxy (the person most familiar with the participant) was given a questionnaire to complete – they may or may not have asked the participant to give them help answering these questions. These forms were mailed back to the study centres.

In order to compile the necessary risk factor information for this particular research, coding guidelines were necessary. Such coding decisions were limited by the location of each variable and the amount of missing information. For baseline risk factor data, the participants' responses to the risk factor questionnaire were used when available. If the participant scored under the cut-off at screening, the proxy risk factor information was taken. Although an agreement study has been carried out by the CSHA Working Group, kappa values for the female sample were calculated in case they differed from the larger sample (See Table 3.3).

Table 3.3: Agreement Between Proxy and Participant Risk Factor Variables

Variable 1	Variable 2	Kappa Value	P-value
Participant RF Down Syndrome	Proxy RF Down Syndrome	1.00	.000
Participant RF Mental Retardation	Proxy RF Mental Retardation	1.00	.000
Participant RF Diabetes	Proxy RF Diabetes	.880	.000
Participant RF Smoker	Proxy RF Smoker	.861	.000
Participant RF Stroke	Proxy RF Stroke	.789	.000
Participant RF Thyroid	Proxy RF Thyroid	.739	.000
Participant RF Parkinson's	Proxy RF Parkinson's	.665	.000
Participant RF Heart	Proxy RF Heart	.664	.000
Participant RF Arthritis	Proxy RF Arthritis	.658	.000
Participant RF High BP	Proxy RF High BP	.636	.000
Participant RF Head Injury	Proxy RF Head Injury	.610	.000
Participant RF Tea	Proxy RF Tea	.585	.000
Participant RF Spirits	Proxy RF Spirits	.584	.000
Participant RF Coffee	Proxy RF Coffee	.579	.000
Participant RF Psychiatric Illness	Proxy RF Psychiatric Illness	.565	.000
Participant RF Alzheimer's	Proxy RF Alzheimer's disease	.559	.000

Participant RF Regular Exercise	Proxy RF Regular Exercise	.539	.000
Participant RF Depression	Proxy RF Depression	.524	.000
Participant RF Epilepsy	Proxy RF Epilepsy	.492	.000
Participant RF Influenza Shot	Proxy RF Influenza Shot	.462	.000
Participant RF Kidney	Proxy RF Kidney	.453	.000
Participant RF Painkiller regular use	Proxy RF Painkiller regular use	.451	.000
Participant RF Wine	Proxy RF Wine	.444	.000
Participant RF Senile Dementia	Proxy RF Senile Dementia	.384	.000
Participant RF Occupational exp to Pesticides	Proxy Occupational Exp to Pesticides	.366	.000
Participant RF Tetanus Shot	Proxy RF Tetanus Shot	.364	.000
Participant RF Polio Shot	Proxy RF Polio Shot	.337	.000
Participant RF Occupational exp to Solvents	Proxy Occupational Exp to Solvents	.279	.000
Participant RF Diptheria Shot	Proxy RF Diptheria Shot	.272	.000
Participant RF Occupational exp to Glues	Proxy Occupational Exp to Glues	.198	.007

Interpretation of the kappa values is as follows: poor (<0.20), fair (0.21 – 0.40), moderate (0.41 – 0.60), good (0.61 – 0.80), and very good (0.81 – 1.00) (131). All values were significant at the $p<.05$ level. The majority of kappa values demonstrate moderate or higher agreement. It is worth acknowledging that kappa is an imperfect measure since it depends on proportion of participants in each category. Nonetheless, it is commonly used and seems to be the most appropriate approach to judging agreement (131).

After combining the participant and proxy information, there still were missing risk factor data. This was a result of participants not returning their questionnaires. In this case, variables from the screening interview, the informant interview, and the clinical assessment where available to fill in only the missing risk factor information. Refer to Appendix B for a detailed breakdown of percentage of data taken from each source to create individual variables. Notably, my initial concerns with using the clinical information, due to its possible superior quality, subsided once I realized the questions I used were predominantly based on self-report from the participant. For some variables, missing information at the previous phase was filled in when the participant responded ‘no’ at the following phase. For example, if the participant answered ‘no’ to ‘have you ever had a heart attack’ at time-2 and this information was

missing at time-1 – then I went back and changed time-1 to 'no'. This could not be done for 'yes' responses, since it was not known when the event occurred.

Kappa values were calculated examining the level of agreement between screening, informant, and clinical data and the newly created risk factor variables. Again, the risk factor variables, which included a combination of self- and proxy-reported data, were used as the core time-1 predictors. However, the degree of missing information made it necessary to use data from other sources. At time-1, screening information was used first to fill in missing values, then clinical data and finally information from the informant. This was done in attempt to use data from the participant first and then from proxy respondents if needed. Although if the participant screened positive for cognitive impairments, the proxy information was favoured. Since at time-2 many of the participants had developed dementia, the informant and clinical variables were used for these individuals.

Table 3.4: Agreement Between Variable Sources (CSHA-1 and –2)

CSHA-1			
RF S&P Diabetes	Informant1 Diabetes	.922	.000
RF S&P Diabetes	Clinical1 Diabetes	.908	.000
RF S&P Diabetes	Screening1 Diabetes	.901	.000
RF S&P Stroke	Informant1 Stroke	.810	.000
RF S&P High BP	Screening1 High BP	.794	.000
RF S&P Parkinson's	Informant1 Parkinson's	.775	.000
RF S&P Stroke	Clinical1 Stroke	.750	.000
RF S&P Parkinson's	Screening1 Parkinson's	.738	.000
RF S&P High BP	Informant1 High BP	.698	.000
RF S&P Stroke	Screen1 Stroke	.613	.000
RF S&P High BP	Clinical1 High BP	.605	.000
RF S&P Heart	Informant1 Heart	.561	.000
RF S&P Heart	Clinical1 Heart	.311	.000
RF S&P Heart	Screen1 Heart	.298	.000
RF S&P Parkinson's	Clinical1 Parkinson's (missing)	------	------
CSHA-2			
Screen2 Diabetes	Clinical 2 Diabetes	.893	.000
Screen2 Diabetes	Informant 2 Diabetes	.882	.000
Screen2 HRT Use	**Nurse/Inform2 HRT Use**	**.802**	**.000**
Screen2 Stroke	Informant 2 Stroke	.587	.000
Screen2 Stroke	Clinical 2 Stroke	.574	.000
Screen2 Parkinson's	Informant 2 Parkinson's	.571	.000
Screen2 High BP	Clinical 2 High BP	.545	.000

Screen2 High BP	Informant 2 High BP	.537	.000
Screen2 Heart	Nurse 2 Heart	.226	.000
Screen2 Heart	Clinical 2 Heart	.217	.000
Screen2 Parkinson's	Clinical 2 Parkinson's	.193	.344

3.4.2.1 HRT Variables

HRT status was assessed during CSHA-2. Female participants were asked, retrospectively, if they had ever used hormones since their menopause or "change in life". This question was used both in the screening interview and in the informant interview. During the latter, HRT status was obtained from either the participant or from a proxy respondent. Although CSHA-2 relied on self and proxy reported use of HRT, past recall of HRT use by participants has been shown to be fairly accurate (155). The informant interview was administered by the study nurses, and therefore was judged to be the most reliable source of information. The nurses' HRT data was used first, but when not available, then the screening interview data was used. There was high agreement between the two data sources (kappa = 0.802). If both the screening interview and the nurse's information report 'yes' HRT has been used, but either had missing or unknown duration or type of hormone; then the available information for either source on duration and type was used.

Information on women's age when the first HRT treatment began, type of hormones used (estrogen and/or estrogen-progesterone combinations), and duration of treatment was retrieved from many participants using HRT. There was a considerable amount of missing data for the type of HRT preparation used and hence this variable will not be used in analysis. This is likely because past users may not have been aware of the whether they have used combination or estrogen-only therapy in previous years, since current users were asked to present the pill packaging. Durations were recorded for each HRT type. For instance, a woman may have changed her HRT prescription several times over the years, and therefore the length of use for each preparation was noted. For the purposes of this research, durations of all HRT preparations used were collapsed into a combined 'length of use' variable. Nonetheless, variables will be included in the models to assess the impact of the timing and duration.

3.4.3 Treating Time-dependent Variables as Time-Independent

The partial likelihood function of Cox Extended model allows for consideration of the effect of time-dependent explanatory variables (156). An explanatory variable is time-dependent if its value for any given individual can change over time. Certain variables in this study fell into this category since with age, the likelihood of health problems increases (eg. emergence of high blood pressure, stroke, heart attack). Even though these variables change over time, it seems appropriate to treat them as time-independent in the analysis if the impact of the change on survival risk depends mainly on the value at only one measurement (156). This meant that Cox Proportional Hazards model was used in place of the Cox Extended model. Therefore, in this study, if two variables were present (measured both at CSHA-1 and-2) then the most recent measure was used in analysis. Since these conditions are generally not reversible, this approach is reasonable. It is also worth noting that some risk factors are more stable; and while some exposures may change, they are likely to have exacted their damage by the time one has entered their senior years. For instance, if an individual quits smoking at age 70, the effects of lifelong smoking habits have likely already done the damage.

3.4.4 Cognitive Status

In an effort to avoid prevalence-incidence bias, only incident cases were included in analysis, thereby excluding dementia and CIND cases present at baseline. For the purposes of this thesis, outcomes include: no cognitive impairment (NCI), CIND, CLoND, VaD, and AD. Participants were classified as NCI when they either scored above the 3MS cut-off at screening or were diagnosed as cognitively normal following neuropsychological and clinical examination. In this dataset, there were a small number of women who screened positive for cognitive impairment (below the 3MS cut-off score) but who did not go onto clinical for a variety of reasons. If the participant participated in the subsequent study phase, the 3MS scores and follow-up diagnoses were used to impute a diagnosis for the previous phase (n=37).

The classification of CIND was used in two ways – all cases together were termed ‘all-cause CIND’ and a ‘reduced CIND’ group was created using only the causes believed to be most closely related to the dementia pathology. This is because CIND is a heterogeneous group, and therefore some causes will likely have a more

similar pathology to Alzheimer disease and vascular dementia. Causes such as Parkinson's disease, age-associated memory impairment, depression, cerebral vascular and general vascular disease will be included in the reduced-cause group; while CIND due to delirium, chronic alcohol abuse, chronic drug intoxication, psychiatric illness (not depression), mental retardation, multiple sclerosis, socio-cultural and blind/deaf causes will be excluded from the secondary analysis. Although several causes may have been specified for each CIND diagnosis at clinical assessment, the primary cause was used for the above classification.

When a participant was diagnosed as either cognitively normal or as having CIND, a secondary distinction was made indicating whether or not there was a significant cognitive decline from the previous phase. Those who experienced this decline were given a CLoND diagnosis. At time-2, there were four CLoND groupings – (1) Cognitively Normal with CLoND, (2) Cognitively Normal without CLoND, (3) CIND with CLOND, and (4) CIND without CLoND. Because most participants with CLoND were also classified as being CIND sufferers (227/248), there were only a very small number of cognitively normal participants with CLoND (21/248). Intuitively, it would seem that the cognitively normal CLoND cases would differ from the CIND CLoND cases. Since sample size was limited for the normal CLoND group, only the CLoND participants from the CIND group were considered for analysis and were compared to the cognitively normal participants without CLoND. Using the same logic as for the reduced-CIND group, the CLoND sample was limited to cases drawn from the reduced-CIND group.

3.4.5 Time-to-Event

Survival analysis was used to identify risk factors associated with AD and VaD, specifically in examining HRT's effect. Here the outcome was time-to-event (in months), with the event being dementia onset. Once the participant was determined to have dementia, follow-up ended for the analysis purpose.

There are several variables in the CSHA that could be used to calculate time-to-onset. In using six variables altogether from the informant and clinical interviews, the time-to-event variable was based on an algorithm proposed and explored in detail by Rouah and Wolfson (157). Rather than taking the mean of all dates provided, a

hierarchical structure was created. This meant that whenever possible, certain variables took precedence over others since they are viewed to be more indicative of the true time-of-onset.

When the time-to-event information was missing for all variables, then a date was imputed. Since a month and year were both required, there was some dates missing a month value; in this case, the seventh month was imputed. A small number of participants were missing the entire date, and when this occurred, the halfway point between study phases was used as time of disease onset. Finally, there were participants who had a negative follow-up time, which meant that time-of-dementia onset was before CSHA-1 and making them ineligible (i.e. prevalent cases). For these participants, it was assumed that the baseline diagnosis was accurate. As a result, if a later, positive date was specified in one of the time-to-onset variables then it was used; if not, then a follow-up time of one month was imputed.

3.5 Data Analysis

3.5.1 Descriptive Analysis

Descriptive analysis was conducted detailing general information about the study sample. This included HRT use, duration of use, type of HRT used, age at first use, prevalence and incidence of cognitive outcomes at each study phase, and description of the samples demographic characteristics. The initial analysis involved a description of the distribution among CIND, CLoND, Alzheimer's disease, vascular dementia and no disease (normal) among HRT users versus never users.

3.5.2 Bivariate

All risk factors were examined for statistically significant associations. Differences between HRT users and non-users were described, and the implications for this study in terms of prevention bias discussed. Pearson’s chi-square test was used to assess significant differences according to HRT status and cognitive status (NCI versus CIND and CLoND). For AD and VaD, potential risk factors were entered one-by-one into the Cox Proportional Hazards survival model to test for significant relationships. Based on this initial analysis of the data, any variable whose bivariate test had a p-value

of equal to or less than 0.25 was considered a candidate for the multivariate model along with all other variables of known biological, clinical, and/or scientific importance.

3.5.3 Multivariate

Analysis was performed using the CSHA-1 and –2 datasets (Refer to Table 3.5). Two different analyses were conducted. First, the Cox Proportional Hazards (PH) Model, a popular survival analysis technique, was conducted using SPSS version10 for MacIntosh (SPSS Inc., Chicago IL)(158). The Cox PH Model can handle missing or censored data while considering the impact of predictor variables on survival times. Rather than simply looking at the presence or absence of an outcome, such as with logistic regression, the Cox Model uses more information by taking into account the time to each event. Participants who are lost to follow-up or who die before the study was completed are classified as censored. Largely due to its robustness as a nonparametric model, this technique is widely used (156). The Cox model was used to assess the risks associated with Alzheimer's disease, and vascular dementia. For this type of analysis, a date of onset of disease must be available. Because a date for CIND and CLoND onset was not available, in so much as it would be hard to distinguish their onset from dementia onset, logistic regression was conducted using SPSS.

Multivariate models were used to examine the combined effect of the various factors of interest adjusting for potential confounders and effect modifiers. This type of analysis will allow for calculation of estimates of the adjusted relative risk, which identifies the risk attributable to the risk factor of interest when risk from the other factor(s) is statistically removed (159).

Table 3.5: Approach to Multivariate Analyses

Outcome	Type of Variable	Statistical Method	Statistical Algorithm	Software
CIND	Dichotomous	Logistic Regression	Maximum Likelihood	SPSS Binary Logistic Regression
CLoND	Dichotomous	Logistic Regression	Maximum Likelihood	SPSS Binary Logistic Regression
Time-to-occurrence of AD or VaD	Survival Type Data	Cox Proportional Hazards Model	Partial Likelihood	SPSS Survival Analysis
Age of AD or VaD onset	Continuous	Linear Regression Analysis	Maximum Likelihood	SPSS Linear Regression

3.6 Ethics

In terms of the larger study, the Coordinating centre in Ottawa obtained ethics approval at each study phase, as did all individual centres. Formal ethics approval for this thesis work was received from the Behavioural Science Research Ethics Board at the University of Saskatchewan (See Appendix A). These data were analyzed in anonymous form, and therefore there are no risks of individual participants being identified.

CHAPTER 4: RESULTS

4.1 Descriptive Analysis

4.1.1 Characteristics of Study Sample: Baseline and First Follow-up Phase

Characteristics of study sample are shown in Table 4.1. At baseline, most participants were 84 years of age and younger, with 49% in the 65-74 age group, 41% in the 75-84 age group, and 10% in the 85 years and older age group. The mean age for women participating was 74.7 years. In terms of education, the average time spent in school was 10.4 years. Sixty percent of this female cohort attended school until grade 10 or higher. Women were sampled equally across the country from the Atlantic (19%), Quebec (21%), Ontario (19%), Prairies (22%), and British Columbia (19%) regions. Most women were currently married (38%) or widowed (49%), while the remainder were either divorced/separated (4%) or had never married (9%). Most of the sample resided in urban centres (89%) and in the community (97%).

During the first follow-up phase (CSHA-2), the same participants were visited and interviewed once again. As expected, most women now belonged to the 75-84 year age group (50%), with fairly equal proportions falling into the 65-74 (27%) and 85 and over (23%) age groups. There was little mobility in terms of the region of residence, however a greater proportion of women were living in institutions (9%) as compared to five years previous (3%). In terms of marital status, 59% of participants were now widowed, leaving fewer married women (28%). As the importance of socioeconomic status was increasingly being recognized, questions regarding current income were included during CSHA-2. Unfortunately, information was not collected on past income or overall adequacy throughout the life course. Nonetheless, the majority of women reported an income less than $19,999 (46%), $20,000-34,999 (21%), $35,000-49,999 (9%), with just 6% of participants reporting income levels at $50,000 or more.

Table 4.1: Sample Characteristics

	CSHA-1 n (%)	CSHA-2 n (%)
65-74 years 75-84 years 85 years & over	1655 (49%) 1396 (41%) 333 (10%) Mean=74.7 yrs SD=6.56	923 (27%) 1687 (50%) 774 (23%) Mean=79.7 SD=6.57
Less than 6 years 7- 9 years 10-12 years 13 years and over	409 (12%) 909 (27%) 1231 (36%) 822 (24%) Mean=10.4 SD=3.48	----------
Less than $19,999 $20,000 – 34,999 $35,000 – 49,999 $50,000 and over	----------	1550 (46%) 718 (21%) 295 (9%) 203 (6%)
Urban Rural	3023 (89%) 353 (10%)	----------
Community Institution	3275 (97%) 109 (3%)	3083 (91%) 301 (9%)
Atlantic Quebec Ontario Prairies British Columbia	649 (19%) 711 (21%) 651 (19%) 744 (22%) 629 (19%)	648 (19%) 708 (21%) 657 (19%) 739 (22%) 632 (19%)
Never Married Married Common Law Divorced/ Separated Widowed	305 (9%) 1281 (38%) 11 (0%) 142 (4%) 1642 (49%)	307 (9%) 954 (28%) 11 (0%) 124 (4%) 1983 (59%)

4.1.2 Cognitive Status

Tables 4.2, 4.3 and 4.4 provide data on cognitive status for each study phase, causes of CIND by study phase, and CSHA-2 CLoND cases. During our first visit and assessment, 93% of our study participants were classified as having no cognitive impairment (NCI) and 7% as having CIND. In an effort to avoid including women with pre-clinical cognitive deficits during time-1, the baseline CIND cases were not used in the multivariate models, but simply included to report baseline cognitive status. Refer to section 3.3 for exclusion and inclusion criteria. The follow-up clinical assessments (CSHA-2) found that 80% of participants had NCI, 12% had CIND, 5% developed

possible or probable AD, 1% had VaD, and an additional 1% fell into the other dementias category. Since risk for cognitive decline is known to rise with age, the increase in the proportion of impairment and disease was anticipated. At baseline, the most commonly identified causes of CIND were age-associated memory impairment (20%), depression (10%), cerebral vascular (7%), and general vascular (6%), although there were a number of CIND cases where the cause was unknown or not specified (45%). A very similar distribution occurred for CIND cases at time-2. CLoND was assessed during CSHA-2 for those who attended clinical and received a NCI or CIND diagnosis. Here participants with CLoND were drawn only from the reduced-cause CIND sample (refer to Methods Section 3.4.4 for more detail).

Table 4.2: Cognitive Status By Study Phase

	CSHA-1 n (%)	**CSHA-2 n (%)**
NCI	3153 (93)	2698 (80)
All-Cause CIND	231 (7)	390 (12)
Possible/Probable AD		161 (5)
Vascular Dementia		41 (1)
Other Dementias		25 (1)

Table 4.3: CIND Causes By Study Phase

	CSHA-1 (n=231) n (%)	**CSHA-2 (n=390) n (%)**
Age-Associated Memory Impairment	47 (20)	69 (18)
Depression	24 (10)	38 (10)
Cerebral Vascular	16 (7)	60 (15)
General Vascular	14 (6)	19 (5)
Parkinson's Disease	1 (0)	8 (2)
Social Isolation	--	10 (3)
Other/ Unknown	105 (45)	113 (29)
Delerium	1 (0)	4 (1)
Chronic Alcohol Abuse and Drug Intoxication	9 (4)	6 (2)
Psychiatric Illness	8 (3)	16 (4)
Mental Retardation	1 (0)	1 (0)
Multiple Sclerosis	1 (0)	1 (0)
Socio-cultural	3 (1)	16 (4)
Blind/Deaf	1 (0)	27 (7)
Epilepsy	--	2 (1)

Table 4.4: CSHA-2 CLoND (n=541)

	HRT Ever n	HRT Never n
NCI-CLoND	5	19
All-Cause CIND-CLoND	57	225
Reduced-Cause CIND-CLoND	50	185

4.1.3 HRT Utilization

In this study sample, 27% of women had used or were currently using HRT, leaving 73% who had never used HRT (refer to table 4.5). This is fairly consistent with the earlier mentioned estimates from the 1994/95 NPHS where 22% of Canadian women 45-64 reported ever using HRT following menopause (31). Of the HRT users, most used estrogen-only preparations (70%) and began using hormones by age 50 (57%). The duration of use varied widely with a number of women using HRT for 12 months or less (25%), and conversely with many using for 10 years or longer (25%).

Table 4.5: HRT Descriptives

HRT Use	**n (%)**
Ever	909 (27)
Never	2475 (73)
HRT Ever Users (n=909)	
Duration	
1 year or less	228 (25)
13 months – 5 years	183 (20)
61 months to 10 years	141 (16)
Over 10 years	225 (25)
Missing	132 (15)
Type of HRT Preparation	
Estrogen Only	633 (70)
Combination	3 (0)
Progestogens Only	17 (2)
Unspecified (“hormones”)	212 (23)
Missing	44 (5)
Age at First HRT Use	
40 years and under	125 (14)
41-50 years	393 (43)
51-60 years	214 (24)
61 years and over	101 (11)
Missing	76 (8)

Looking at incident cognitive outcomes according to HRT status (table 4.7), a greater proportion of HRT users had the lesser diagnosis NCI (90%) as compared to HRT never users (83%). However, HRT never users had more CIND (11% versus 7%), AD (4% versus 2%), and VaD (1% versus .3%) as compared to ever users.

Table 4.6: CSHA-2 Cognitive Status According to HRT Use (Prevalent and Incident Cases)

	HRT Users n (%)	**HRT Never Users n (%)**
NCI	791 (88)	1907 (79)
CIND	72 (8)	318 (13)
AD	27 (3)	134 (6)
VaD	3 (.3)	38 (2)
Other Dementias	8 (1)	26 (1)

Table 4.7: CSHA-2 Cognitive Status According to HRT Use (Incident Cases Only)

	HRT Users n (%)	**HRT Never Users n (%)**
NCI	785 (90)	1885 (83)
CIND	59 (7)	245 (11)
AD	19 (2)	93 (4)
VaD	3 (.3)	26 (1)
Other Dementias	4 (1)	20 (1)

4.2 Bivariate Analysis

4.2.1 Covariate Identification For Multivariate Analysis

Bivariate analysis was used to determine which variables to include in the multivariate models. According to the standard approach, any variable with a p-value equal to or less than 0.25 will be included in multivariable analysis. As discussed previously, Pearson's chi-square test was used for the variable CIND and the Cox model was used to test variables for significance for AD and VaD. All outcome variables were dichotomous – presence or absence of impairment/ disease. Table 4.8 lists all variables significant at the $p<.25$ level for the outcomes all-cause CIND, reduced CIND, reduced-CLoND, AD, and VaD. For a more detailed breakdown of this analysis see Appendix C.

Table 4.8: Covariates significant at the p<.25 level: results of bivariate analyses for CSHA-2

Potential Covariates	**All-cause CIND**	**Reduced CIND**	**Reduced CLoND**	**AD**	**VaD**
Demographics					
Age	√	√	√	√	√
Education	√	√	√	√	√
Income	√	√	√	√	√
Residential Status T-1 and -2	√	√	√	√	√
Marital Status T-1 and –2	√	√	√	√	√
Rural-Urban				√	√
Region T-1 and-2	√	√	√	√	
Health Conditions and Illness					
Arthritis		√			
Thyroid Condition	√	√	√	√	
Heart Attack					√
Kidney Disease	√	√	√		√
Epilepsy	√	√		√	√
Diabetes T-1 and -2	√				
Stroke T-1 and -2	√	√	√	√	√
High Blood Pressure T-1 and -2	T2 only	T2 only	√	√	√
Parkinson's Disease T-1 and-2	√	√	√	T2 only	T2 only
Depression T-1 and -2	√	√	√	√	√
Psychiatric Illness	√	√	√		√
Medication Use					
HRT Use	√	√	√	√	√
HRT Duration		√	√		N/A
Age at First HRT Use					N/A
Regular Painkiller Use			√		√
Current Use of Statins	√	√	√		N/A
Lifestyle Factors					
Regular Coffee	√			√	
Regular Tea				√	
Regular Wine	√	√	√	√	
Regular Spirits	√	√	√	√	√
Regular Shellfish Consumption		√	√	√	√
Regular Exercise	√	√	√	√	√
Smoking Status	√	√	√	√	√
Vitamin B					
Vitamin C	√	√	√	√	
Vitamin E	√	√	√	√	N/A
Multi-vitamin	√	√	√	√	

History of Head Injury					√
Familial and Genetic Factors					
APOE Status				√	√
Family History of AD	√	√	√	√	
Family History of Senile Dementia		√		√	
Family History of Mental Retardation	√				N/A
Family History of Down Syndrome		√	√		N/A
Other Exposures					
Influenza Shot(s)					
Polio Shot(s)	√	√	√	√	√
Diptheria Shot(s)	√	√	√	√	√
Tetanus Shot(s)	√	√	√	√	√
Occupational Exposure to Solvents				√	
Occupational Exposure to Pesticides		√	√		
Occupational Exposure to Glues					

T2 only – Significant only at CSHA-2; NA- not enough cases to test; √ - significant at the $p< 0.25$ level

In terms of demographic variables, age, marital status, education, income, and residential status were consistently significant for all outcomes. Both AD and VaD differed significantly by rural-urban status, while region was significant for all outcomes except VaD.

When testing a variety of different health conditions and illnesses for significant contributions to each outcome, there was substantial variability. However, stroke, high blood pressure, Parkinson's disease, and depression were significant for all outcomes. Psychiatric illness was significant for both CIND outcomes, CLoND, and VaD, but not for AD.

HRT was significantly associated with all outcomes. Duration of HRT use was found to be significant only for the reduced-CIND and CLoND groups, although neither duration nor age at first use had sufficient VaD cases to test for an association.

Many of the lifestyle factors were found to be significantly associated with the outcome measures. At the $p<.25$ level, regular consumption of coffee, tea, wine, spirit, and shellfish, exercise, smoking, and current vitamin C, E, and multi-vitamin intake were all related to AD. Only regular spirit and shellfish consumption, exercise, and smoking status were found to be significant for VaD. There was much overlap between the CIND groups and AD. Similarly, variables significant for reduced-CIND showed the same for reduced-CLoND. One unexpected finding was for history of head injury,

which only revealed significance for VaD. APOE status, a definite risk factor for dementia, was found to differ ($p<.25$) according to AD and VaD outcomes; however, this genetic risk factor was not significant for the CIND or CLoND groups. Immunizations, including polio, diptheria, and tetanus, were associated with all outcomes. The variables vitamin B and occupational exposure to glues were the only two factors that did not show to be significant for any of the outcomes.

Notably, bivariate analysis was only used for selecting statistically significant variables to be included in model building and multivariate analysis. These findings did not control for the effects of age and other relevant factors, hence they were simply correlated with the outcomes and do not indicate causal relationships.

4.2.2 Comparison Between HRT Users and Never Users

In an effort to identify significant differences between HRT users and never users, Pearson's Chi-square test was used to examine a variety of factors. These factors may help to identify important differences between these two groups; variations that may contribute to cognitive health outcomes. Using bivariate analysis, the following factors differed significantly ($p<.25$) according to HRT use: heart attack, other heart condition, diabetes-2, thyroid disease, arthritis, kidney disease, epilepsy, depression at time-1, psychiatric illness; age, marital status, education, income, region, residential status, rural/urban status; smoking status, regular consumption of wine, spirits, coffee, and shellfish, exercise, current vitamin E, C, and multi-vitamin intake; painkiller and statin use; and immunizations for influenza, polio, diptheria, and tetanus.

Looking in more detail at the distribution of HRT users and never users according to each risk factor, some trends were evident ($p<.05$). In terms of physical health, a greater proportion of HRT users had thyroid conditions, arthritis, and kidney disease than never users. HRT users also belonged more often to the younger age groups and were more likely to be currently married than the never user group. A greater proportion of HRT users were living in Quebec and British Columbia, while more never users resided in the Atlantic region. HRT use differed according to residential status, with a greater proportion of never users living in institutions as compared to users. In general, the bivariate analysis found that lifestyle factors differed according to HRT use. HRT users were more likely to smoke regularly and to drink spirits, wine, and coffee

than never users. Moreover, a greater number of HRT users engage in regular exercise, take painkillers, and use vitamins E, C, and multi-vitamins. Finally, more HRT users received immunizations (influenza, diptheria, polio, and tetanus) than never users.

4.3 **Multivariate Analysis**

4.3.1 **Model Building Strategy**

Hosmer and Lemeshow's (160) model building strategy was employed for the analysis of all outcomes. In an attempt to fit a best model, backward stepwise elimination was carried out manually using the 'enter' method. First, all relevant independent variables were entered into the model. These included factors that were significant ($p<.25$) in bivariate analysis and other biologically or clinically important factors. When the sample size permitted, I erred on the side of being over-inclusive since this investigation was somewhat explorative in nature. The vascular dementia model was the exception here since the small number of cases required that covariates be kept to the minimum. After fitting a model with all significant covariates, variables that were removed earlier from the model were re-entered to ensure they did not add to the model. The result was a main effects model where significant ($p<.05$) and clinically important predictors remained. Next, all possible interaction terms were entered into the model one-at-a-time. The interaction terms were retained if the Wald statistic was significant at the $p<.05$ level. Confounding was assessed by comparing the ß values of important predictors in the reduced main effects model to those in a model including the potential confounder. A change greater than 20% in ß values between models was an indication of confounding, and hence the confounder was retained in the model. Once the final model was constructed, it was assessed for goodness of fit using the likelihood ratio test (161).

4.3.2 Prevention Bias: HRT Ever Users as Compared to HRT Never Users

4.3.2.1 Predictors of HRT Use

Binary logistic regression was used to further explore the differences between HRT ever and never user groups. The final main effects model identified several predictors significant at the $p<.05$ level. Refer to Table 4.9 below. As expected, the likelihood that one would have used HRT decreased with increasing age. Women belonging to the younger age groups were much more likely to have used HRT as compared to women in the 85 years and older category. When compared to women in the lowest income category ($19,999 or less), those participants with higher incomes ($35,000 or more) were more likely to report HRT use. There were also regional differences in HRT Use. For instance, women living in Quebec were more likely than British Columbia residents to have used HRT. In terms of overall health, women without diabetes were more likely than women with diabetes to have used HRT. Conversely, women with a thyroid condition, arthritis, or a kidney condition were more likely to report HRT use. Current use of vitamin E or multi-vitamin supplements were also predictors of HRT use, with women who currently use these vitamins being more likely to report HRT use. Women who had received flu shot(s) were more likely than women not receiving a flu shot to have used HRT. There are clear differences in relevant predictors between HRT users and never users. These differences may account for some of the HRT effect on cognition. Such variations need to be taken into account in analysis.

4.3.2.2 Model Diagnostics

To assess the goodness of fit of the model, the likelihood ratio (LR) test was used. The LR test subtracts the LR statistics from the full and reduced models, thereby examining whether the final or reduced model is significantly a better fit than the larger, more inclusive model. For the model presented in Table 4.9, the log likelihood statistic was highly significant (LR=675.33. $\chi 2_{31} = 52.62$, $p<0.001$). This indicates that the final main effects model was the better, more parsimonious model. As a result, the model is acceptable.

Table 4.9: Final Main Effects Model: HRT Never Use Versus HRT Ever Use

Variable (reference)	**ß (S.E.)**	**Sig.**	**Exp (ß)**	**95% C.I. for Exp (B)**	
				Lower	**Upper**
Age					
65-74 years	1.287 (.176)	.000	3.621	2.565	5.110
75-84 years	.753 (.165)	.000	2.123	1.537	2.933
85 years + (ref)		.000			
Arthritis (no)	.394 (.112)	.000	1.483	1.191	1.848
Current Vitamin E Use (no)	.493 (.183)	.007	1.638	1.144	2.344
Current Multi-Vitamin Use (no)	.405 (.132)	.002	1.499	1.157	1.942
Diabetes-2 (yes)	.501 (.180)	.005	1.650	1.160	2.346
Income					
$19,999 or less (ref)		.043			
$20,000-34,999	.215 (.127)	.090	1.240	.967	1.589
$35,000 + (ref)	.337 (.142)	.018	1.400	1.060	1.849
Influenza Shots (no)	.246 (.106)	.021	1.279	1.038	1.575
Kidney Disease (no)	.437 (.160)	.006	1.548	1.131	2.119
Region					
Atlantic	-.315 (.174)	.071	.730	.519	1.028
Quebec	.318 (.159)	.045	1.374	1.006	1.876
Ontario	-.201 (.165)	.221	.818	.592	1.129
Prairies	-.141 (.153)	.359	.869	.644	1.173
British Columbia (ref)		.003			
Regular Spirit Consumption (no)	.272 (.133)	.042	1.312	1.011	1.703
Stroke-2 ((no)	.422 (.208)	.043	1.525	1.014	2.292
Thyroid Condition (no)	.391 (.124)	.002	1.478	1.159	1.884

*Exp(ß) can be interpreted as a measures of odds ratios, which is an approximation of relative risk.

4.3.3 All-Cause CIND

4.3.3.1 Independent Variables

The relationship between HRT and all-cause CIND was examined using logistic regression, while controlling for other covariates. There were 304 incident cases of all-cause CIND and 2670 participants with NCI included in this model. Once the participants' with missing data were removed from the model, 210 CIND cases and 1794 normal participants remained for analysis. A number of predictors were found to be significant (See Table 4.10). Consistent with the literature, there is a dose-response relationship between age and educational attainment and CIND, with lower education and advanced age considerably increasing one's risk. Women in the 85 and older age

group were almost seven times more likely than those in the 65-74 age group to have all-cause CIND (OR=7.13); while women from ages 75-84 remained at an increased, but lower, risk (OR=2.368). Participants with a history of stroke or Parkinson's disease were over three times more likely than participants without these conditions to be diagnosed with all-cause CIND. Women reporting a history of psychiatric illness (including anxiety) and current depression were more likely to have all-cause CIND, although depression was of borderline statistical significance (p=.051). In terms of residential status, individuals who resided in an institution were almost five times more likely than those living in the community to have been diagnosed with all-cause CIND. Both family history of Alzheimer's disease and mental retardation were found to increase one's risk. Conversely, regular exercise, use of NSAIDs, and regular consumption of shellfish were found to protect for cognitive impairment. HRT status did not reach significance in this model. HRT duration was then tested for significance, first in finer categories (1 year or less; more than 1 year up to 5 years; more than 5 years up to 10 years; more than 10 years) and then collapsed into a more broad classification (no use; 5 years or less; greater than 5 years). Neither of the two duration variables was found to be a significant predictor of all-cause CIND.

Table 4.10: Final Main Effects Model: Cognitively Normal Versus All-Cause CIND

Variable (reference group)	**ß (S.E.)**	**Sig.**	**Exp (ß)**	**95% C.I. for Exp (ß)**	
				Lower	**Upper**
Age					
65-74 years (ref)		.000			
75-84 years	.862 (.252)	.001	2.368	1.447	3.878
85 years +	1.964 (.268)	.000	7.129	4.219	12.046
Current Depression (no)	.458 (.235)	.051	1.581	.998	2.505
Education					
6 years & under	1.255 (.536)	.019	3.508	1.226	10.035
7- 9 years	.991 (.466)	.033	2.693	1.081	6.713
10-12 years	-.496 (.503)	.325	.609	.227	1.634
13 years + (ref)		.001			
Family History of AD (no)	1.914 (.503)	.000	6.781	2.529	18.183
Family History of Mental Retardation (no)	.928 (.454)	.041	2.529	1.040	6.152
HRT (yes)	.265 (.483)	.583	1.304	.506	3.360

NSAID Use (yes)	.681 (.239)	.004	1.977	1.238	3.156
Parkinson's Disease-2 (no)	1.314 (.410)	.001	3.722	1.668	8.307
Psychiatric Illness (no)	.473 (.191)	.014	1.604	1.102	2.334
Regular Consumption of Shellfish (yes)	.629 (.246)	.011	1.876	1.157	3.041
Regular Exercise (yes)	1.049 (.341)	.002	2.854	1.464	5.563
Residential Status (community)	1.049 (.341)	.000	4.679	2.656	8.242
Stroke-2 (no)	1.242 (.252)	.000	3.462	2.113	5.672
HRT*Education		.023			
6 years or less*HRT	.625 (.619)	.313	1.868	.555	6.286
7-9 years*HRT	-.361 (.552)	.513	.697	.236	2.058
10-12 years*HRT	1.149 (.577)	.047	3.156	1.018	9.786
HRT*Family History AD	-1.325 (.594)	.026	.266	.083	.852
HRT*Regular Exercise	-.823 (.391)	.035	.439	.204	.944

*Exp(ß) can be interpreted as a measures of odds ratios, which is an approximation of relative risk.

Final Model for All-cause CIND

Log (p/1-p) = $\beta 0$ + $\beta 1$(age 75-84) + $\beta 2$ (age 85+)+ $\beta 3$ (depression) + $\beta 4$ (educ <=6 yrs) + $\beta 5$ (educ 7- 9 yrs) + $\beta 6$ (educ 10-12 yrs) +$\beta 7$ (family history of AD) + $\beta 8$ (family history of mental retardation) + $\beta 9$ (HRT use) + $\beta 10$ (NSAID use) + $\beta 11$ (Parkinson's disease) + $\beta 12$ (psychiatric illness) + $\beta 13$ (shellfish) + $\beta 14$ (regular exercise) + $\beta 15$ (residential status) + $\beta 16$ (stroke) + $\beta 17$ (Educ <+6 yrs*HRT) + $\beta 18$ (educ 7-9 yrs*HRT) + $\beta 19$ (Family history of AD* HRT) + $\beta 20$ (Regular exercise*HRT)

*Where p=probability of occurrence of all-cause CIND.

4.3.3.2 Interaction Assessment

In the final model, HRT status was found to interact with the variables *regular exercise, educational attainment, and family history of AD.* Cross-tabulations were initially carried out in order to ascertain a descriptive view of the type of relationship that exists between these interacting variables.

4.3.3.2.1 HRT-Education Interaction

Table 4.11: Cognitively Normal Participants and HRT-Education Interaction (n=2661)

	EDUCATION n (%)			
	6 years or less	**7 - 9 years**	**10-12 years**	**13 years +**
HRT User	69 (9)	182 (23)	311 (40)	222 (28)
HRT Never User	173 (9)	508 (27)	703 (38)	493 (26)

Table 4.12: All-Cause CIND and HRT-Education Interaction (n=303)

	EDUCATION n (%)			
	6 years or less	**7 - 9 years**	**10-12 years**	**13 years +**
HRT User	14 (24)	22 (37)	11 (19)	12 (20)
HRT Never User	59 (24)	64 (26)	88 (36)	33 (14)

Looking at women with all-cause CIND (Table 4.12), one can observe a trend where a higher proportion of HRT users fall into the highest level (13 years or more) of educational attainment as compared to never users. The lowest level of education is known to put individuals at the highest risk for dementia, however the proportion of women having 6 years or less of education was the same for both groups. Therefore differences in educational attainment between the two groups may have little impact on the outcome of CIND. Notably, a greater proportion of HRT users (37%) fall into the 7-9 years of education category as compared to HRT never users (26%). This educational level seems to also confer risk for cognitive decline, albeit not as much as the 6 year or less category.

4.3.3.2.2 HRT-Exercise Interaction

Table 4.13: Cognitively Normal Participants and HRT-Exercise Interaction (n=2340)

	Regular Exercise n (%)	
	Yes	**No**
HRT User	508 (72)	202 (29)
HRT Never User	1087 (67)	543 (33)

Table 4.14: All-Cause CIND and HRT-Exercise Interaction (n=262)

	Regular Exercise n (%)	
	Yes	**No**
HRT User	25 (48)	27 (52)
HRT Never User	112 (53)	98 (47)

When assessing the interaction effect between HRT status and exercise in the normal sample (Table 4.14), HRT users appear somewhat more likely to exercise regularly as compared to never users (72% vs. 67%). The opposite is true for the all-cause CIND group, where more HRT never users exercised regularly as compared to users (53% vs. 48%).

4.3.3.2.3 HRT-Family History of AD Interaction

Table 4.15: Cognitively Normal and HRT-Family History of AD Interaction (n=2135)

	Family History of AD n (%)	
	Yes	**No**
HRT User	38 (6)	620 (94)
HRT Never User	93 (6)	1384 (94)

Table 4.16: All-Cause CIND Participants and Family History of AD Interaction (n=241)

	Family History of AD n (%)	
	Yes	**No**
HRT User	8 (14)	620 (86)
HRT Never User	25 (11)	1384 (90)

By breaking down the interaction effect between HRT status and family history of AD, one can see that a slightly greater proportion of HRT users with all-cause CIND have a family history of AD as compared to never users (Refer to Table 4.16).

Table 4.17: Calculation of Odds Ratios for All-Cause CIND When Interaction Present

Effect	**Among**	**Exp (β)**	**95% CI**
Education*			
6 years or <	HRT Users	3.51	1.26 – 10.04
7-9 years	HRT Users	2.69	1.08 – 6.71
10-12 years	HRT Users	0.61	0.23 – 1.63
6 years or <	HRT Never Users	6.55	3.49 – 12.29
7-9 years	HRT Never Users	1.88	1.34 – 3.78
10-12 years	HRT Never Users	1.92	1.14 – 3.23
HRT Never Users**	6 years or <	2.44	0.95 – 6.23

HRT Never Users	7-9 years	0.91	0.52 – 1.58
HRT Never Users	10-12 years	4.11	1.68 – 10.10
HRT Never Users	13 years +	1.30	0.51 – 3.360
Exercise**			
No Regular Exercise	HRT Users	2.85	1.46 – 5.56
No Regular Exercise	HRT Never Users	1.25	.085 – 1.86
HRT Never Users	No Regular Exercise	0.57	0.17 – 1.93
HRT Never Users	Yes Regular Exercise	1.30	0.51 – 3.36
Family History of AD***			
Yes History	HRT Users	6.78	2.53 – 18.18
Yes History	HRT Never Users	1.80	1.00 – 3.24
HRT Never Users	Yes History	0.35	0.09 – 1.31
HRT Never Users	No History	1.304	0.51 – 3.36

* Reference group is HRT users with 13 years or more education

** Reference group is HRT users who exercise regularly.

*** Reference group is HRT users without a family history of AD.

When interactions were present, calculations of odds ratios for all-cause CIND were carried out according to Hosmer and Lemeshow's approach (160). Through this technique, it was found that educational level significantly increased one's risk for a diagnosis of CIND in both user groups, with the exception of the 10-12 year category in HRT users (Table 4.17). When comparing HRT never users to users, it appeared that low education (6 years or less) more than doubled never users risk for CIND (OR=2.44), although this association was only borderline significant. Women belonging to the 10-12 year educational category who had never used HRT were at a substantially increased risk (OR=4.11) for CIND as compared to users with similar education. In terms of HRT's interaction with regular exercise, it seemed that lack of regular exercise increased HRT users risk for CIND (OR=2.85), but the same was not true for the HRT never users. Finally, looking at family history of AD and its interaction with HRT, it was found that having a family history of AD greatly increased

HRT users risk for CIND (OR=6.78), but did not have the same significant effect on HRT never users.

4.3.3.3 Confounding

Potential confounders were entered into the model and the ß-values were compared between models with and without the variable. If the difference in the ß-values was greater than 20% or if it changed the statistical significance of the primary independent variable, then confounding was present. Age, residential status, NSAID use, and education were all identified as confounders; since they were already in the model as covariates, the model did not change. However, depression was borderline not significant, but remained in the model due to its confounding effect.

4.3.3.4 Model Diagnostics

To assess the goodness of fit of the model, the likelihood ratio test was used. For this present model, the log likelihood statistic was significant (LR=374.47. $\chi 2_{32}$ = 52.62, $p<0.001$). This indicates that the final main effects model fit better than the full model, which contained more variables. As a result, the model is acceptable.

4.3.4 Reduced-Cause CIND

4.3.4.1 Independent Variables

Logistic regression was used to examine the relationship between HRT and reduced-cause CIND while controlling for covariates. Many factors achieved significance (Table 4.18). Similar to the more inclusive all-cause CIND outcome, there is a dose-response relationship between age and educational attainment and reduced-cause CIND. Women with up to 6 years of education were over three times as likely to receive a reduced-cause CIND diagnosis as compared to those with 13 or more years; while women with 7-9 years remained at an increased risk, albeit lower (OR=2.36). Participants with a history of stroke or Parkinson's disease were over three times more likely than participants without these conditions to be diagnosed with reduced-cause CIND. Depression was highly significantly related to reduced-cause CIND, with current depression doubled one's risk of a diagnosis. Psychiatric illness did not reach significance, as it did for the all-cause CIND outcome. This is likely due to the fact that CIND caused by psychiatric illness was removed from the reduced-cause group. In

terms of residential status, individuals who resided in an institution were almost four times more likely than those living in the community to have been diagnosed with all-cause CIND. Family history of Alzheimer's disease, but not of mental retardation, was found to increase one's risk. Regular exercise and use of NSAIDs were protective. HRT status was not a significant predictor of reduced-cause CIND, nor was duration of HRT use (p=.731).

Table 4.18: Final Main Effects Model: Cognitively Normal Versus Reduced-Cause CIND

Variable (reference group)	**β (S.E.)**	**Sig.**	**Exp (B)**	**95% C.I. for Exp (β)**	
				Lower	**Upper**
Age-2					
65-74 years		.000			
75-84 years	.863 (.256)	.001	2.369	1.436	3.910
85 years + (ref)	1.919 (.273)	.000	6.813	3.987	11.643
Current Depression	.804 (.218)	.000	2.235	1.457	3.429
Education					
6 years & under	1.202 (.504)	.017	3.328	1.239	8.940
7- 9 years	.946 (.438)	.031	2.576	1.091	6.084
10-12 years	-.625 (.492)	.204	.535	.204	1.405
13 years + (ref)		.001			
Family History of AD (no)	1.780 (.467)	.000	5.929	2.376	14.799
HRT (yes)	-.196 (.424)	.644	.822	.358	1.887
NSAID Use (yes)	.557 (.235)	.018	1.745	1.101	2.765
Parkinson's Disease-2 (no)	1.289 (.421)	.002	3.628	1.589	8.283
Regular Exercise (yes)	.442 (170)	.009	1.556	1.115	2.171
Residential Status (community)	1.357 (.289)	.000	3.886	2.208	6.841
Stroke-2 (no)	1.233 (.247)	.000	3.433	2.116	5.569
HRT*Education		.011			
6 years or less*HRT	.603 (.596)	.311	1.828	.568	5.878
7-9 years*HRT *HRT	-.410 (.534)	.443	.664	.233	1.889
10-12 years*HRT	1.250 (.568)	.028	3.490	1.146	10.630
HRT*Family History AD	-1.581 (.590)	.007	.206	.065	.654

*Exp(ß) can be interpreted as a measures of odds ratios, which is an approximation of relative risk.

Final Model for Reduced-cause CIND

$$\text{Log } (p/1\text{-}p) = \beta_0 + \beta_1(\text{age 75-84}) + \beta_2 (\text{age 85+}) + \beta_3 (\text{depression}) + \beta_4 (\text{educ <=6 yrs}) + \beta_5 (\text{educ 7- 9 yrs}) + \beta_6 (\text{educ 10-12 yrs}) + \beta_7 (\text{family history of AD}) + \beta_8 (\text{HRT use}) + \beta_9 (\text{NSAID use}) + \beta_{10} (\text{Parkinson's disease}) + \beta_{11} (\text{regular exercise}) + \beta_{12} (\text{residential status}) + \beta_{13} (\text{stroke}) + \beta_{14} (\text{Educ <+6 yrs*HRT}) + \beta_{15} (\text{educ 7-9 yrs*HRT}) + \beta_{15} (\text{Family History AD*HRT})$$

*Where p=probability of occurrence of reduced-cause CIND.

4.3.4.2 Interaction Assessment

As with the all-cause CIND model, HRT status was found to interact with *educational attainment* and *family history of AD*. The interaction between HRT and exercise was not significant in this model. Cross-tabulations were carried out in order to determine the type of relationship that exists between these variables.

4.3.4.2.1 HRT-Education Interaction

Table 4.19: Cognitively Normal Participants and HRT-Education Interaction (n=2661)

	EDUCATION			n (%)
	6 years or less	**7 - 9 years**	**10-12 years**	**13 years +**
HRT User	69 (9)	182 (23)	311 (40)	222 (28)
HRT Never User	173 (9)	508 (27)	703 (38)	493 (26)

Table 4.20: Reduced-Cause CIND Participants and HRT-Education Interaction (n=247)

	EDUCATION			n (%)
	6 years or less	**7 - 9 years**	**10-12 years**	**13 years +**
HRT User	12 (23)	20 (38)	10 (19)	11 (21)
HRT Never User	49 (25)	48 (25)	69 (36)	28 (14)

When looking at the reduced-cause CIND sample (Table 4.20), one can notice a trend where HRT users fall into the highest levels of educational attainment as compared to never users. Here 21% of HRT users had 13 or more years of education, while only 14% of never users belonged to this category. In addition, a greater proportion of HRT users (38%) fell into the 7-9 years of education category as compared to HRT never users (25%). Although the proportions differ slightly, the same type of HRT-education interaction appears in both the reduced- and all-cause CIND models.

4.3.4.2.2 HRT-Family History of AD Interaction

Table 4.21: Cognitively Normal Participants and HRT-Family History of AD Interaction (n=2135)

	Family History of AD n (%)	
	Yes	**No**
HRT User	38 (6)	620 (94)
HRT Never User	93 (6)	1384 (94)

Table 4.22: Reduced-Cause CIND Participants and HRT-Family History of AD Interaction (n=241)

	Family History of AD n (%)	
	Yes	**No**
HRT User	8 (16)	43 (84)
HRT Never User	15 (8)	175 (92)

An interaction effect between HRT status and family history of AD was not found for the cognitively normal sample (Table 4.21). Although for women in the reduced-cause group (Table 4.22), it seems that a greater proportion of HRT users had a family history of AD as compared to HRT never users (16% versus 8%). This interaction effect is similar to that observed with the all-cause CIND group, however it is more pronounced.

Table 4.23: Calculation of Odds Ratios for Reduced-Cause CIND When Interaction Present

Effect	**Among**	**Exp (β)**	**95% CI**
Education*			
6 years or <	HRT Users	3.33	1.24 – 8.94
7-9 years	HRT Users	2.58	1.09 – 6.08
10-12 years	HRT Users	0.54	0.20 – 1.41
6 years or <	HRT Never Users	6.08	3.27 – 11.30
7-9 years	HRT Never Users	1.71	0.92 – 3.18
10-12 years	HRT Never Users	1.87	1.07 – 3.25
HRT Never Users**	6 years or <	1.50	0.63 – 3.61
HRT Never Users	7-9 years	0.55	0.28 – 1.08
HRT Never Users	10-12 years	2.87	1.31 – 6.28
HRT Never Users	13 years +	0.82	0.36 – 1.89

Family History of AD**			
Yes History	HRT Users	5.93	2.38 – 14.80
Yes History	HRT Never Users	1.22	0.64 – 2.34
HRT Never Users	Yes History	0.17	0.05 – 0.61
HRT Never Users	No History	0.82	0.36 – 1.89

* Reference group is HRT users with 13 years or more education

** Reference group is HRT users without a family history of AD.

As with the all-cause CIND model, hand calculations were completed in order to calculate odds ratios for each level of interaction (Refer to Table 4.23). The interactional effects found in the reduced model were very similar to the all-cause CIND model. Educational level significantly increased one's risk for a diagnosis of CIND in both user groups, with the exception of the 10-12 year category in HRT users and a borderline not significant association for HRT never users in the 7- 9 year category. When comparing HRT never users to users, only the 10-12 year educational level significantly increased never users risk over that of users (OR=2.87). The borderline significant association seen for those with 6 years of education or less in the all-cause CIND model disappeared in the reduced-cause model. Then looking at family history of AD and its interaction with HRT, a family history of AD greatly increased HRT users risk for CIND (OR= 5.93), but did not have the same significant effect on HRT never users.

4.3.4.3 Confounding

Potential confounders were entered into the model and the ß-values were compared between models with and without the variable. Age, depression, residential status, NSAID use, education, and exercise were all identified as confounders; however since they were already in the model as covariates, the model did not change.

4.3.4.4 Model Diagnostics

To assess the goodness of fit of the model, the likelihood ratio test was used. For this present model, the log likelihood statistic was significant (LR=463.48. $\chi 2_{32}$= 52.62, $p<0.001$). This indicates that the final main effects model was the better, more parsimonious model. As a result, the model is a very good fit.

4.3.5 CLoND

4.3.5.1 Independent Variables

By using logistic regression, HRT was examined for an association with CLoND. After adjusting for the effects of other important covariates, HRT status did not show a significant effect on the CLoND outcome (See Table 4.24). When broken down into duration of use, the results were the same (p=.854). However, numerous other variables were found to be significant predictors for CLoND. Age and educational attainment were both strongly associated with cognitive loss. As with the two previous model CIND models, both illustrated a dose-response relationship with the outcome. Participants with a history of stroke or Parkinson's disease were over three times more likely than participants without these conditions to be diagnosed. Interestingly, thyroid conditions appeared to be protective. Depression was highly significantly related to CLoND, where current depression almost tripling one's risk. In terms of residential status, individuals who resided in an institution were three times more likely than those living in the community to have received a CLoND diagnosis. Family history of Alzheimer's disease was found to greatly increase one's risk. When using British Columbia as the reference category, women living in Quebec and Ontario were at higher risk. When the Quebec region was used as the comparison group, the Prairies and B.C. were found to be at a lower risk. Quebec had the highest proportion of CLoND cases out of all the regions. Although marital status was included only as a confounder, it seems that women who were divorced or separated were at an increased risk for CLoND. Conversely, regular exercise, use of NSAIDs, and regular consumption of shellfish were protective.

Table 4.24: Reduced Main Effects Model: Cognitively Normal Versus CLoND

Variable (reference group)	β **(S.E.)**	**Sig.**	**Exp (β)**	95% C.I. for Exp (B) Lower	Upper
Age-2					
65-74 years (ref)		.000			
75-84 years	1.052 (.317)	.001	2.864	1.538	5.335
85 years +	2.205 (.347)	.000	9.074	4.599	17.902

Current Depression (no)	.990 (.242)	.000	2.691	1.675	4.325
Education					
6 years & under	1.215 (.348)	.000	3.371	1.703	6.671
7- 9 years	.619 (.299)	.039	1.856	1.032	3.338
10-12 years	.374 (.285)	.190	1.454	.831	2.544
13 years + (ref)		.005			
Family History of AD (no)	1.612 (.535)	.003	5.012	1.756	14.309
HRT (yes)	.138 (.240)	.565	1.148	.717	1.839
Marital Status-2					
Married/Common Law (ref)		.096			
Separated/Divorced	1.137 (.477)	.017	3.117	1.224	7.940
Widowed	.289 (.273)	.288	1.336	.783	2.279
Never Married	.011 (.408)	.978	1.011	.455	2.251
NSAID Use (yes)	.783 (.279)	.005	2.188	1.265	3.783
Parkinson's Disease-2 (no)	1.396 (.481)	.004	4.039	1.574	10.361
Region					
Atlantic	.512 (.346)	.139	1.668	.847	3.288
Quebec	.845 (.318)	.008	2.328	1.249	4.339
Ontario	.691 (.334)	.038	1.997	1.038	3.842
Prairies	-.176 (.352)	.617	.838	.420	1.672
British Columbia (ref)		.004			
Regular Exercise (yes)	.470 (.192)	.015	1.599	1.097	2.332
Regular Shellfish Consumption (yes)	.564 (.285)	.048	1.757	1.005	3.074
Residential Status (community)	1.115 (.335)	.001	3.048	1.581	5.876
Stroke-2 (no)	1.195 (.282)	.000	3.304	1.901	5.742
Thyroid Condition (no)	-.612 (.282)	.030	.542	.312	.942
HRT*Family History of AD	-1.353 (.666)	.042	.258	.070	.953

*Exp(ß) can be interpreted as a measures of odds ratios, which is an approximation of relative risk.

Final Model for CLoND

$$\text{Log } (p/1\text{-}p) = \beta_0 + \beta_1(\text{age 75-84}) + \beta_2(\text{age 85+}) + \beta_3(\text{depression}) + \beta_4(\text{educ <=6 yrs}) + \beta_5(\text{educ 7- 9 yrs}) + \beta_6(\text{educ 10-12 yrs}) + \beta_7(\text{family history of AD}) + \beta_8(\text{HRT use}) + \beta_9(\text{family history of mental retardation}) + \beta_{10}(\text{Separated/Divorved}) + \beta_{11}(\text{Widowed}) + \beta_{12}(\text{Never Married}) + \beta_{13}(\text{NSAID use}) + \beta_{14}(\text{Parkinson's disease}) + \beta_{15}(\text{region, Atlantic}) + \beta_{16}(\text{region, Quebec}) + \beta_{17}(\text{region, Ontario}) + \beta_{18}(\text{region, Prairies}) + \beta_{19}(\text{regular exercise}) + \beta_{20}(\text{regular shellfish}) + \beta_{21}(\text{residential status}) + \beta_{22}(\text{stroke}) + \beta_{23}(\text{thyroid condition}) + \beta_{24}(\text{Family History of AD*HRT})$$

*Where p=probability of occurrence of CLoND.

4.3.5.2 Interaction Assessment

In the final model, HRT status was found to interact with family history of Alzheimer's disease. Cross-tabulations were carried out in order to ascertain the type of relationship that exists between these interacting variables.

4.3.5.2.1 HRT-Family History of Alzheimer's Disease Interaction

Table 4.25: Cognitively Normal Participants and HRT-Family History of AD Interaction (n=2128)

	Family History of AD n (%)	
	Yes	**No**
HRT User	38 (6)	619 (94)
HRT Never User	93 (6)	1378 (94)

Table 4.26: CLoND Participants and HRT-Family History of AD Interaction (n=195)

	Family History of AD n (%)	
	Yes	**No**
HRT User	7 (17)	35 (83)
HRT Never User	14 (9)	139 (91)

Looking at women with CLoND (Table 4.26), one can detect a trend where a greater proportion of HRT Users have a family history of AD as compared to never users. It is believed that having a family history of AD increases one's risk for cognitive decline and impairments. From this data, one would be unable to discern if a family predisposition towards AD influences women's decision to use or not use HRT. Interaction between HRT and education was assessed and the term was borderline not significant (p=.059), and therefore it was removed from the model.

Table 4.27: Calculation of Odds Ratios for CLoND When Interaction Present

Effect	**Among**	**Exp (β)**	**95% CI**
Family History of AD*			
Yes History	HRT Users	3.37	1.70 – 6.67
Yes History	HRT Never Users	1.30	0.59 – 2.84
HRT Never Users	Yes History	0.30	0.09 – 1.01
HRT Never Users	No History	1.148	0.72 – 1.84

* Reference group is HRT users without a family history of AD.

Hand calculations assessing the interaction effect between HRT and family history of AD in the CLoND model found that family history of AD significantly increased risk for CLoND in HRT users (Refer to Table 4.27). This association was not identified in the HRT never user group. This finding was also seen in the all- and reduced-cause CIND models. Almost reaching significance, HRT never users with a family history of AD were less likely to have CLoND as compared to HRT users with a family history of AD.

4.3.5.3 Confounding

Marital status was tested positive for confounding and therefore was included in the model as a confounder. Age, depression, residential status, regular exercise, and NSAID use were all identified as confounders; however since they were already in the model as covariates, the model did not change.

4.3.5.4 Model Diagnostics

To assess the goodness of fit of the model, the likelihood ratio test was used. For this present model, the log likelihood statistic was significant (LR=322.90. $\chi 2_{32}$ = 52.62, $p<0.001$). This indicates that the final main effects model was the better, more parsimonious model. As a result, the model is a very good fit.

4.3.6 Alzheimer's Disease

4.3.6.1 Independent Variables

Cox PH Model was used to examine the relationship between HRT and AD. Refer to section 3.4.5 for an explanation of time-to-event and censoring used in this approach. There were 112 incident cases of AD and 2670 participants with NCI included in this model. Once the participants' missing data was removed from the model, 89 AD cases and 1944 censored participants remained for analysis. After controlling for other covariates, HRT status was statistically significant ($p<.05$) (Table 4.28). HRT never users were over ten times as likely as users to have developed AD in the study's five-year follow-up period. Interestingly, HRT duration was not significant ($p=.257$). However, when plotted on a survival curve (see Figure 2) the results seem to indicate a trend for use less than five years to be protective, whereas use longer than 5 years and no use at all confer similar risk. Consistent with the findings of previous

studies, both depression and high blood pressure were found to increase risk for AD. Risk for AD was found to increase with age. Specifically, the risk was doubled for those in the 75-84 age group and almost nine times greater for those 85 and over, as compared to women 65-74 years of age. Regular wine consumption, past tetanus shots, and residing in a rural area appeared protective. Women who had never been married were also at a decreased risk for developing AD when compared to those who are currently married, although being divorced, separated or widowed did not have a significant effect.

Some variables had relatively rare events, which makes it difficult to assess their effect on the outcome. However, upon further examination it could be seen that there was only one instance in the AD sample; therefore sample size would have prevented a more accurate estimate. In addition, marital status initially showed a peculiar confidence interval indicating small numbers in each cell, therefore the divorced/ separated and widowed categories were collapsed to increase the number of cases in each cell. This stabilized the estimates, while retaining the significance of the predictor.

Table 4.28: Final Main effects for Alzheimer's disease: Cox Proportional Hazards Model

Variable (reference group)	**β (S.E.)**	**Sig.**	**Exp (B)**	**95% C.I. for Exp (β)**	
				Lower	**Upper**
Age-2					
65-74 years (reference)		.000			
75-84 years	.8441 (.461)	.068	2.318	.939	5.720
85 years +	2.170 (.475)	.000	8.761	3.451	22.245
Current Depression (no)	.619 (.301)	.040	1.858	1.029	3.354
Education					
6 years & under	1.375 (1.436)	.338	3.955	.237	66.005
7- 9 years	2.650 (1.102)	.016	14.161	1.632	122.884
10-12 years	1.501 (1.113)	.178	4.485	.506	39.752
13 years + (ref)		.045			
High Blood Pressure-2 (no)	.528 (.220)	.017	1.695	1.101	2.610
HRT (yes)	2.316 (1.047)	.027	10.134	1.301	78.946
Marital Status					
Married (ref)		.013			
Divorced/Separated//Widowed	-.278 (.309)	.368	.757	.414	1.387
Never Married	-1.579 (.545)	.004	.206	.071	.600
Regular Wine Consumption (yes)	1.162 (.522)	.026	3.196	1.149	8.885

Residential Status (community)	2.331 (.247)	.000	10.291	6.347	16.686
Rural-Urban Status (Urban)	-.957 (.473)	.043	.384	.152	.971
Tetanus Immunization (Yes)	.968 (.361)	.007	2.633	1.297	5.345
HRT*Education		.045			
6 years or less*HRT	-1.335 (1.482)	.368	.263	.014	4.802
7-9 years*HRT	-2.952 (1.146)	.010	.052	.006	.494
10-12 years*HRT	-1.932 (1.152)	.094	.145	.015	1.386

*Exp(ß) is the hazards ratio obtained from the survival model. It can be interpreted as a measure of odds ratios, which is an approximation of relative risk.

The survival curve (see Figure1 below) illustrates the different interactions between HRT use and level of education and their effects on the AD outcome. This graph is adjusted for all other predictors included in the Cox PH model. The vertical axis plots the cumulative survival of the study sample, ho here because AD is a rare event. In terms of the whole study sample, a very small proportion of individuals developed AD in this five-year period. It appears that HRT never users as a group had quite similar survival times, as compared to HRT users, where level of education seemed to effect AD survival. Unfortunately, a line could not be plotted for the interaction between HRT and the highest level of education (13 years +), since there were too few cases.

Figure 1. Interaction Effects between HRT Status and Education and Survival of Women with AD

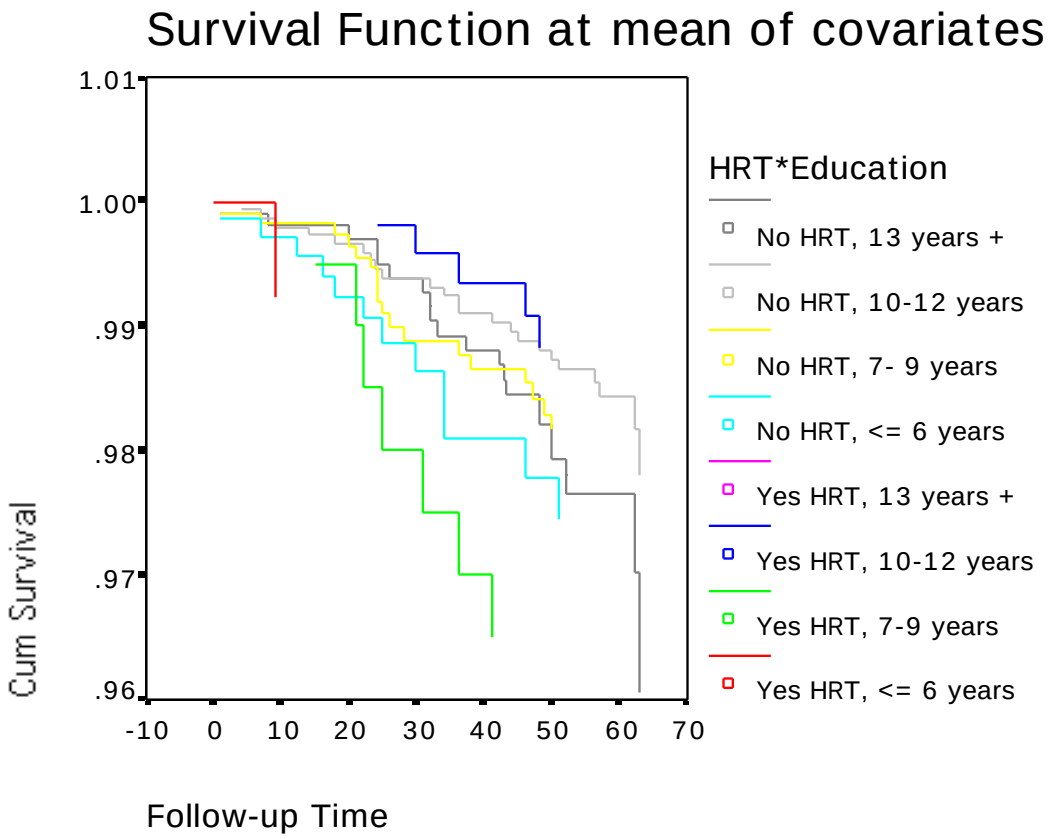
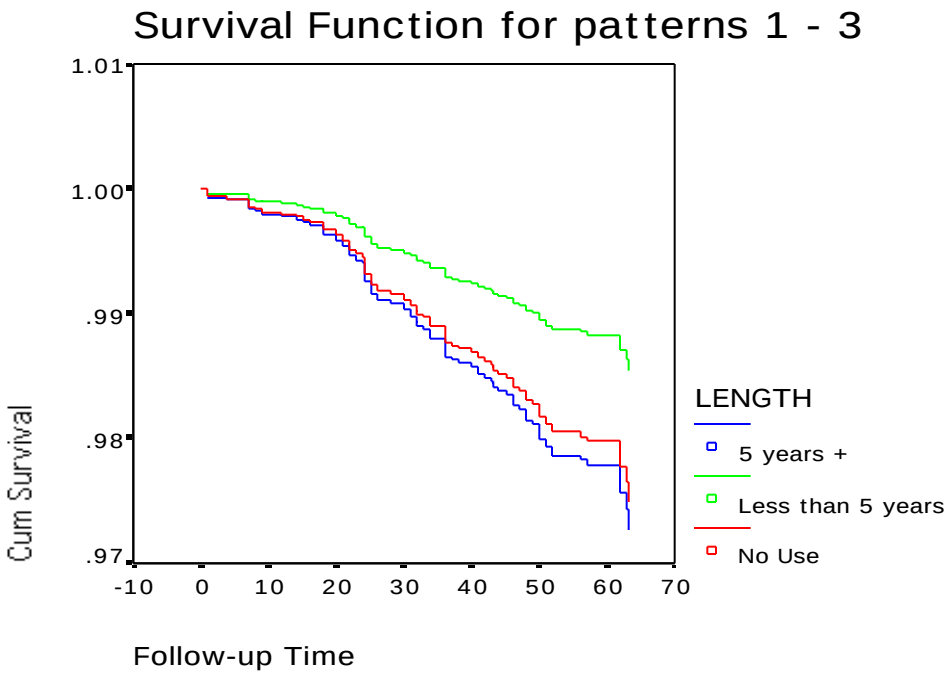


Figure 2. Duration of HRT Use and Survival of Women with AD



4.3.6.2 Interaction Assessment

All possible interaction terms were tested after fitting the main effects model. Interestingly, the previously observed interaction between HRT use and family history of AD did not appear significant. As with the other models, HRT status was found to interact with education.

4.3.6.2.1 HRT-Education Interaction

Table 4.29: Cognitively Normal Participants and HRT-Education Interaction (n=2661)

	EDUCATION n (%)			
	6 years or less +	**7 - 9 years**	**10-12 years**	**13 years**
HRT User	69 (9)	182 (23)	311 (40)	222 (28)
HRT Never User	173 (9)	508 (27)	703 (38)	493 (26)

Table 4.30: Alzheimer's Disease and HRT-Education Interaction (n=111)

	EDUCATION n (%)			
	6 years or less	**7 - 9 years**	**10-12 years**	**13 years +**
HRT User	1 (5)	9 (47)	8 (42)	1 (5)
HRT Never User	13 (14)	25 (27)	29 (32)	25 (27)

For the AD group, HRT users fall more heavily into the categories 7-9 and 10-12 years (See Table 4.30). Whereas HRT never users are more normally distributed throughout all levels of educational attainment, with a sizeable proportion having completed 13 or more years of schooling (27%). HRT users had a smaller proportion of individuals in the highest and lowest levels of education than HRT never users. Importantly, the smaller number of HRT users in the AD group (n=19), and particularly within each educational category, makes it difficult to assess the interaction effect and to know if the effect would remain with a larger number of cases.

Table 4.31: Calculation of Hazard Ratios for Alzheimer's Disease When Interaction Present

Effect	**Among**	**Exp (β)**	**95% CI**
Education*			
6 years or <	HRT Users	3.96	0.24 – 66.01
7-9 years	HRT Users	2.65	1.63 – 122.89
10-12 years	HRT Users	4.49	0.51 – 39.75
6 years or <	HRT Never Users	1.04	0.50 – 2.17
7-9 years	HRT Never Users	0.74	0.40 – 1.37
10-12 years	HRT Never Users	0.65	0.35 – 1.21
HRT Never Users**	6 years or <	2.67	0.34 – 21.03
HRT Never Users	7-9 years	0.53	0.22 – 1.30
HRT Never Users	10-12 years	1.47	0.55 – 3.91
HRT Never Users	13 years +	10.13	1.30 – 78.95

* Reference group is HRT users with 13 years or more education

** Reference group is HRT users

Further exploration into the nature of the interaction between HRT and education was done for the AD outcome. The 7- 9 years educational level significantly increased HRT user's risk for AD, however the same was not true for never users. When comparing HRT never users to HRT users, the 13 years or greater category greatly increased never user's risk for AD as compared to HRT users with a similar level of education. This was the only educational level to achieve statistical significance. Notably, there are low numbers in the 6 year or less and 13 years or more educational categories for HRT users (see table 4.30). This means that the observed interaction effect must be interpreted cautiously and further study of this interaction in studies with sufficient sample size is necessary.

4.3.6.3 Confounding

All potential confounders were assessed. Age, marital status, and residential status were shown to be confounding factors; since they were already significant risk factors the model remained unchanged. Stroke, Parkinson's disease, rural-urban status, psychiatric illness, head injury, NSAID use, Family History of AD, and smoking were all tested for confounding; they were not shown to be confounding factors.

4.3.6.4 Model Diagnostics

4.3.6.4.1 Goodness of Fit

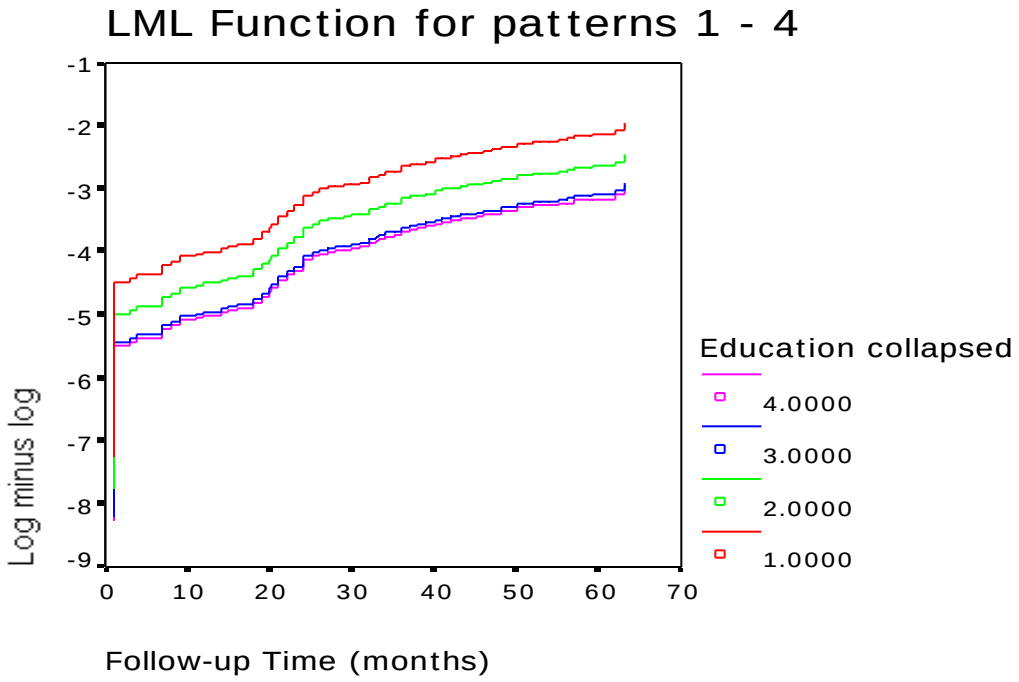
To assess the goodness of fit of the model, the likelihood ratio test was used. For this present model, the log likelihood statistic was significant (LR=590.46. $\chi 2_{23} = 49.73$, $p<0.001$). This indicates that the final main effects model was the better, more parsimonious model as compared to the full model containing a greater number of variables.

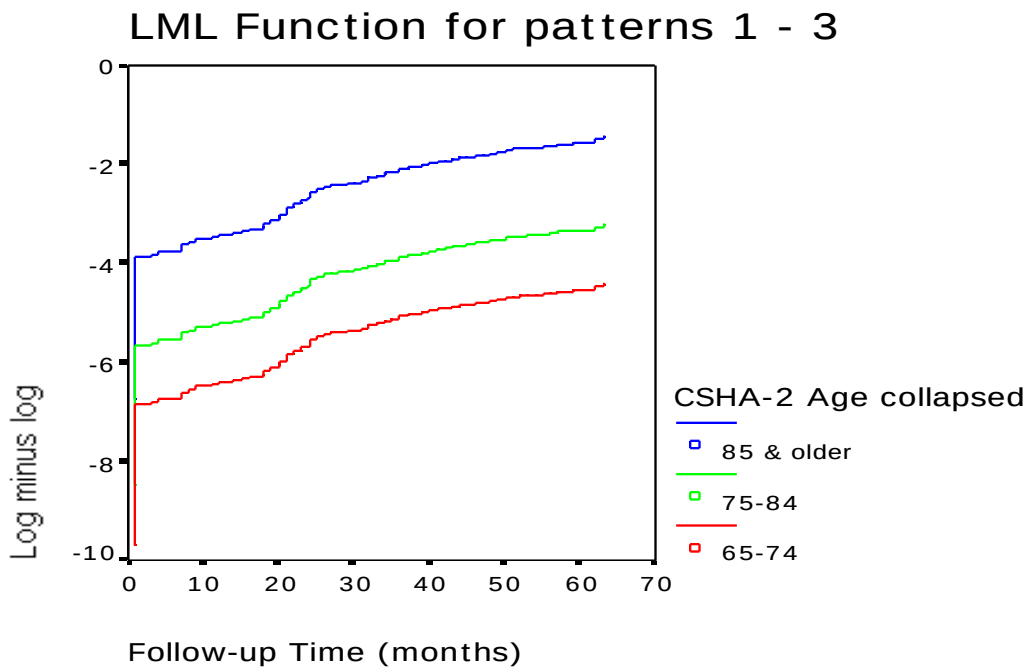
4.3.6.4.2 Proportional Hazards Assumption

When using the Cox PH Model it is important that the covariates meet the Proportional Hazards assumption. This means that the hazard for an individual is comparative to the hazard for any other individual over time (156). Put another way, the effect of a given covariate must not change over time. There are different ways – both graphical and numerical -- that the assumption can be assessed. There is no known evidence today that one approach is better than another at assessing the PH

assumption (162). There are different ways that the PH assumption can be checked. One of the most popular methods is to use log-log survival curves (156). If once the curve is plotted, the lines are parallel then the assumption is met. Log-log survival curves were computed for important variables and those at high risk for violating the PH assumption. This included HRT status, age, education, diabetes, stroke, depression (Refer to Figure 3); as well as head injury, tetanus, and high blood pressure (Figures not shown). All variables tested met the PH assumption.

Figure 3. Log Minus Log Plots: Education, Age, HRT, Diabetes, Stroke, and Depression

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Log minus log
0
-2
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-6
-8
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40
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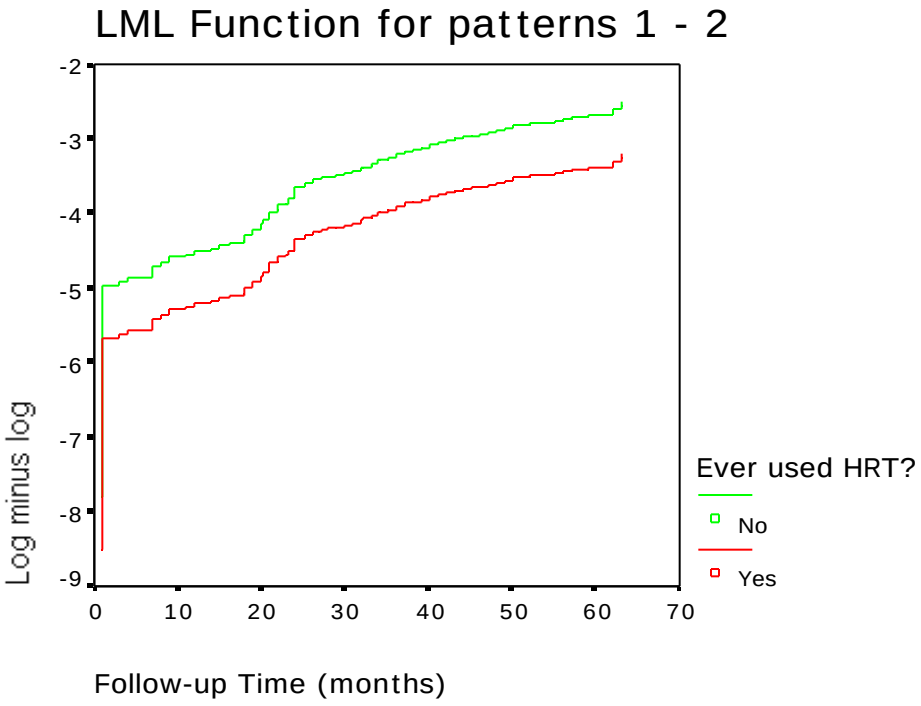
60
70
Follow-up Time (months)
CSHA-2 Age collapsed
85 & older
75-84
65-74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-4
-5
-6
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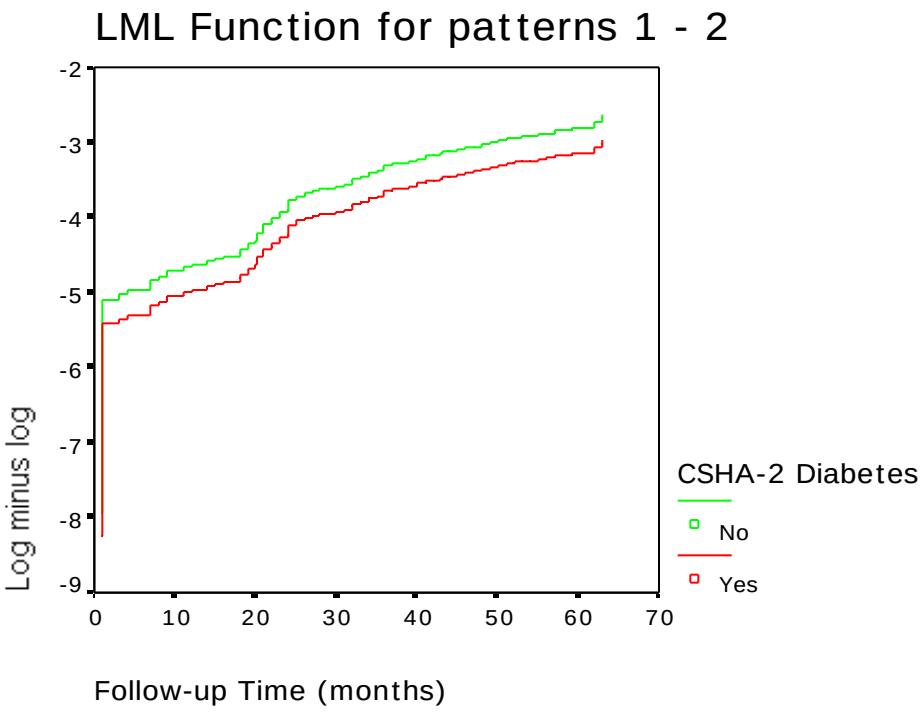
0
10
20
30
40
50
60
70
Follow-up Time (months)
Ever used HRT?
No
Yes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Log minus log
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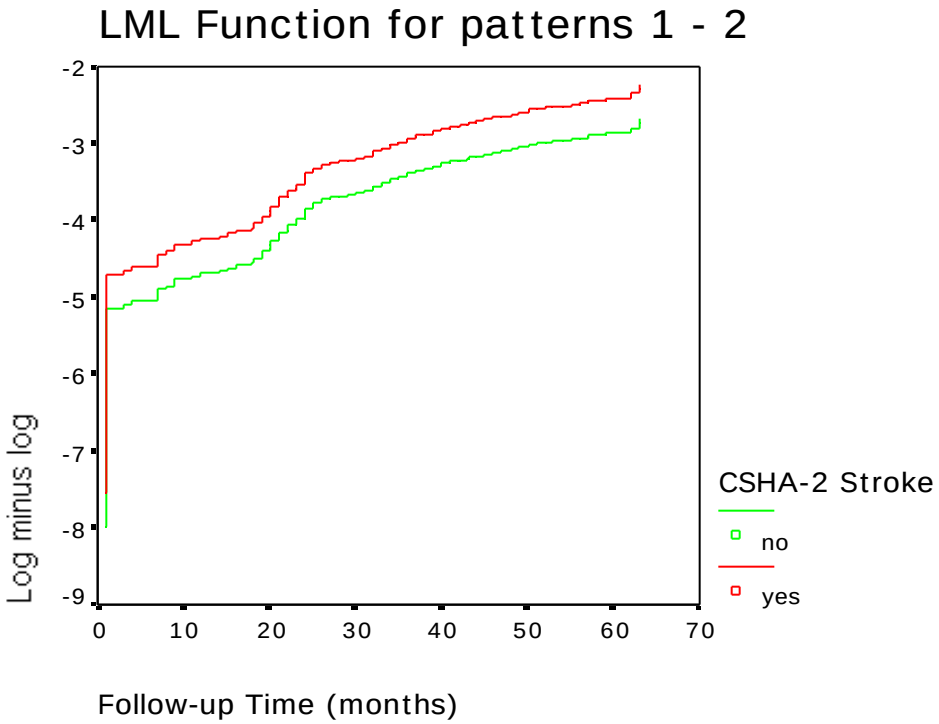
70
Follow-up Time (months)
CSHA-2 Diabetes
No
Yes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Log minus log
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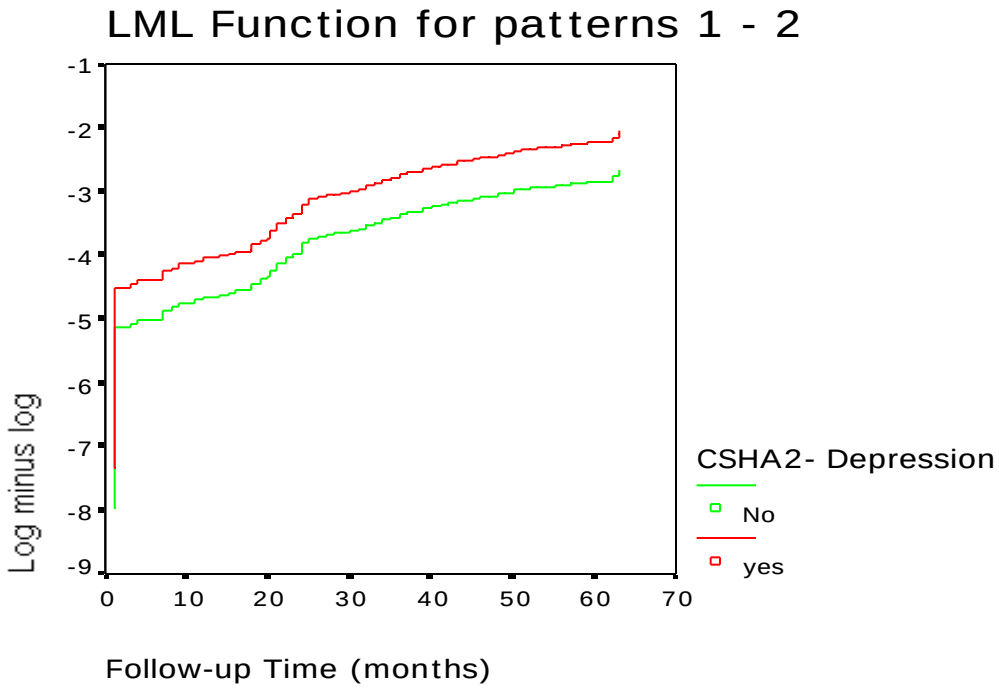
70
Follow-up Time (months)
CSHA-2 Stroke
no
yes



4.3.7 Alzheimer's Disease and Age at Onset

4.3.7.1 Linear Regression Model

Using a linear regression model, the effect of HRT on age of AD onset was assessed. Here the dependent variable was age at AD onset. HRT status initially was found to significantly predict for age of disease onset when entered alone into the model. However, once the continuous variable for age was added, HRT status was no longer a significant predictor for age of AD onset. No other variables entered into the model were found to be significant.

Table 4.32: Final Main Effects Model: Predictors of Age of AD Onset

Variable (reference)	**β (S.E.)**	**Sig.**	**95% C.I. for Exp (β)** **Lower**	**Upper**
Age-2	1.069 (.049)	.000	.971	1.167
HRT (yes)	.384 (.789)	.628	-1.182	1.949

4.3.8 Vascular Dementia

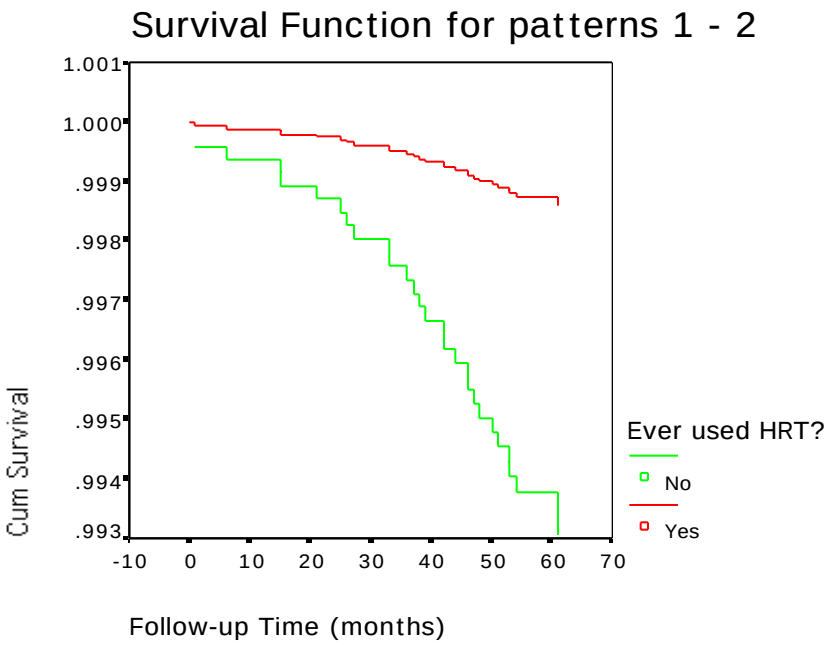
4.3.8.1 Independent Variables

Using the Cox PH Model, the relationship between HRT and VaD was examined. HRT status was shown to be significant with a large effect size (Table 4.33). That is, HRT never users were five times more likely to have developed VaD in the five-year follow-up period. Figure 4 graphically illustrates this relationship. The impact of HRT duration on VaD could not be assessed due to small numbers. Upon closer inspection of the data using crosstabulation, one can see that only three of the 26 VaD cases used HRT at all and two of these cases had used for longer than 5 years. Therefore the less than 5 years HRT duration category was empty making analysis of duration impossible for this outcome. As with all other models, age and education were also significant predictors. Because of the limited overall number of VaD cases in the final model, it was necessary to treat age as a continuous variable and to further collapse education into two categories (6 years and under, 7 years and over). Current depression, history of high blood pressure, and living in an institution all were found to be significant.

Table 4.33: Final Main Effects Model for Vascular Dementia: Cox Proportional Hazards Model

Variable (reference group)	**β (S.E.)**	**Sig.**	**Exp (B)**	**95% C.I. for Exp (β)**	
				Lower	**Upper**
Age-2	.068 (.031)	.030	1.070	1.007	1.137
Current Depression (no)	1.242 (.406)	.002	3.462	1.563	7.669
Education (7 years+)	1.079 (.439)	.014	2.943	1.244	6.960
High Blood Pressure-2 (no)	1.311 (.438)	.003	3.711	1.572	8.760
HRT (yes)	1.606 (.744)	.031	4.985	1.160	21.411
Residential Status (community)	2.632 (.434)	.000	13.903	5.943	35.524

Figure 4. HRT Status and Survival of Women with VaD



4.3.8.2 Interaction Assessment

Variables were assessed for interaction, however no terms reached significance.

4.3.8.3 Confounding

Tests for confounding were limited by sample size considerations. However, high blood pressure, residential status, current depression, age and education were all found to confound the relationship between HRT and VaD. Since all these factors were already included in the model as risk factors, the model remained the same.

4.3.8.4 Model Diagnostics

4.3.8.4.1 Goodness-of-fit

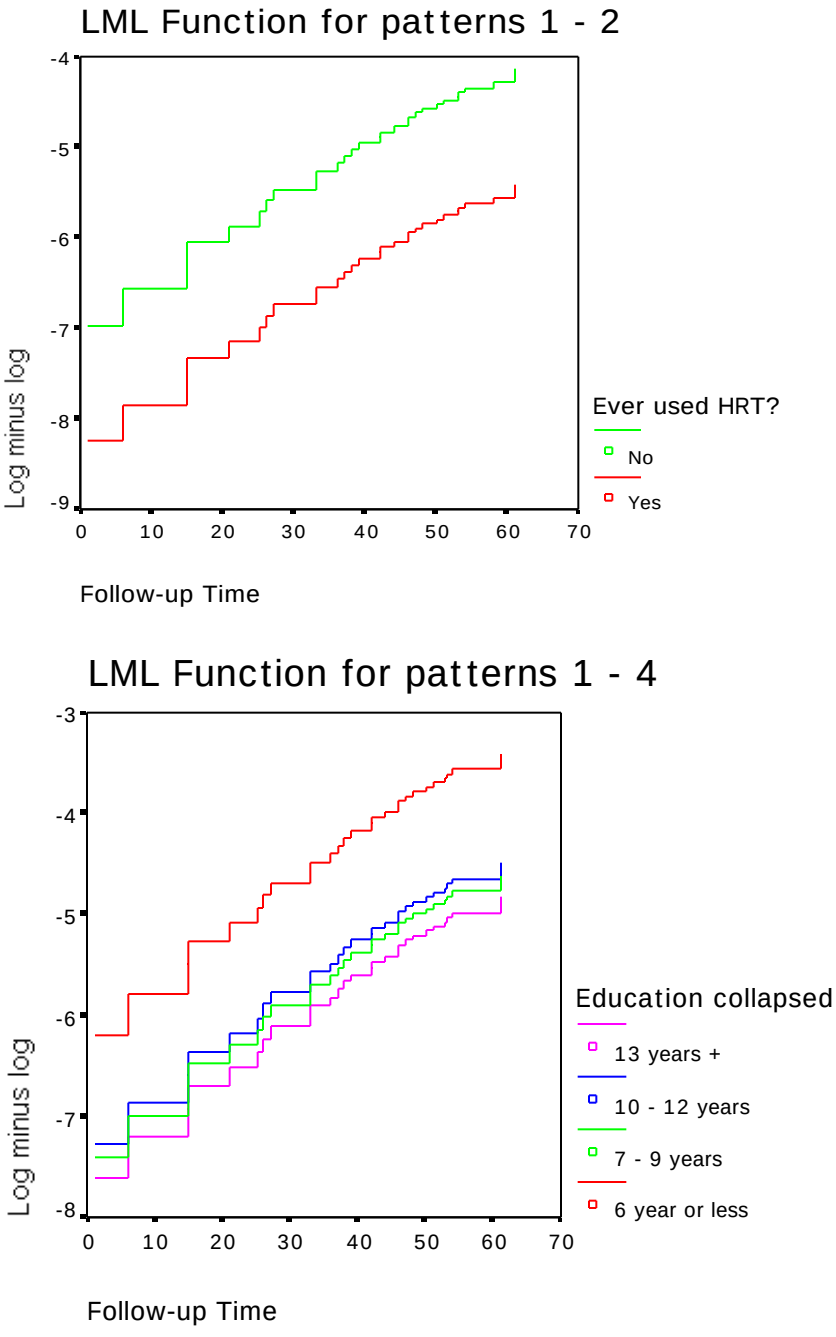
To assess the goodness of fit of the model, the likelihood ratio test was used. For this present model, the log likelihood statistic was significant (LR=317.31. $\chi 2_{26}$ = 52.62, $p<0.001$). As a result, the model is accepted as the better fit as compared to the fuller, more inclusive model.

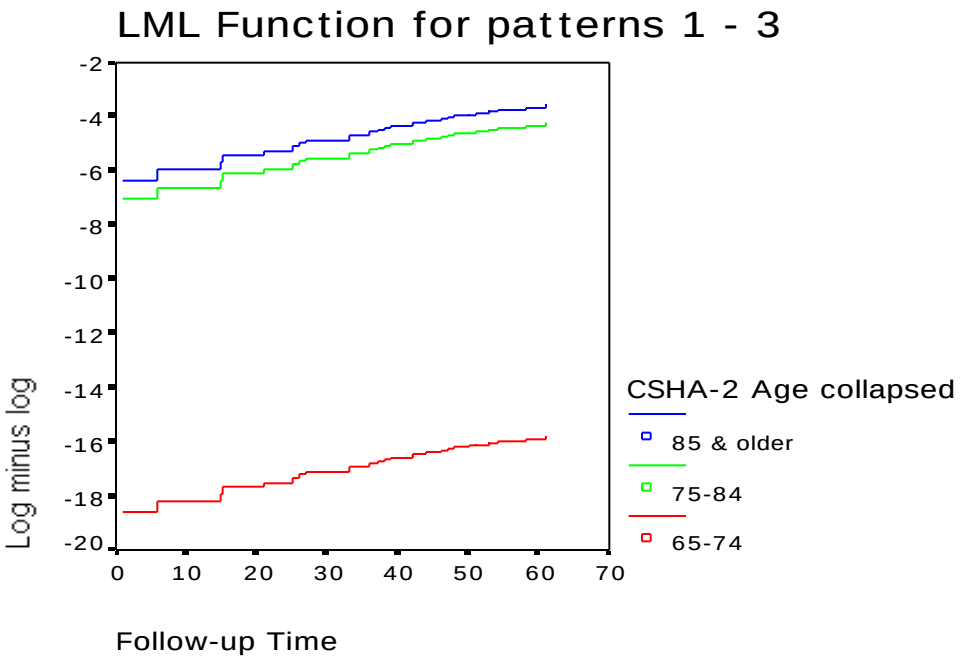
4.3.8.4.2 Proportional Hazards Assumption

Covariates were entered into the Cox PH Model one at-a-time in order to ensure the PH assumption was met. As illustrated by the parallel lines in each plot, the

assumption was met for all of the significant predictors including HRT use, educational attainment, age, residential status and depression (See Figure 5).

Figure 5. Log Minus Log Plots: HRT, Education, Age, Residential Status, Depression and High Blood Pressure

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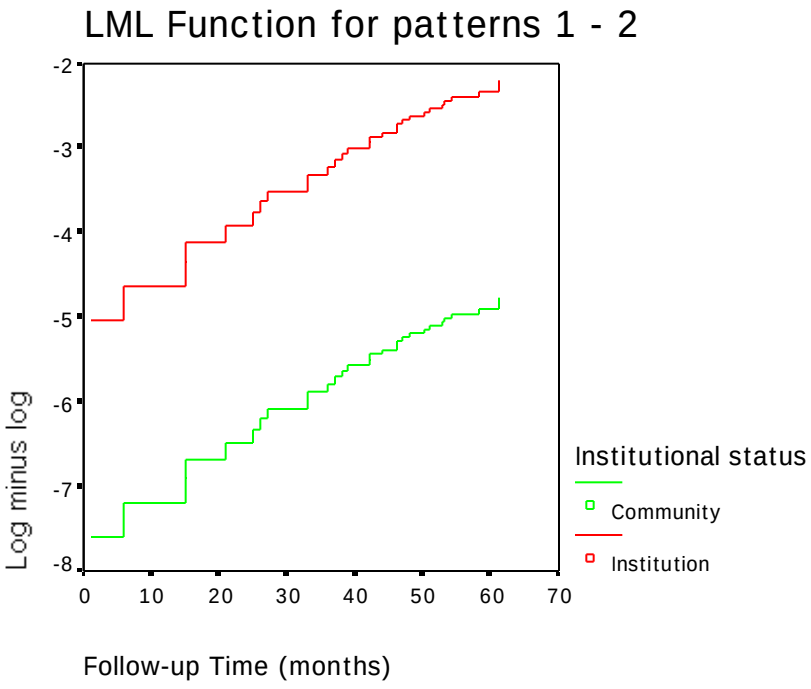
70
Follow-up Time
CSHA-2 Age collapsed
85 & older
75-84
65-74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Log minus log
0
10
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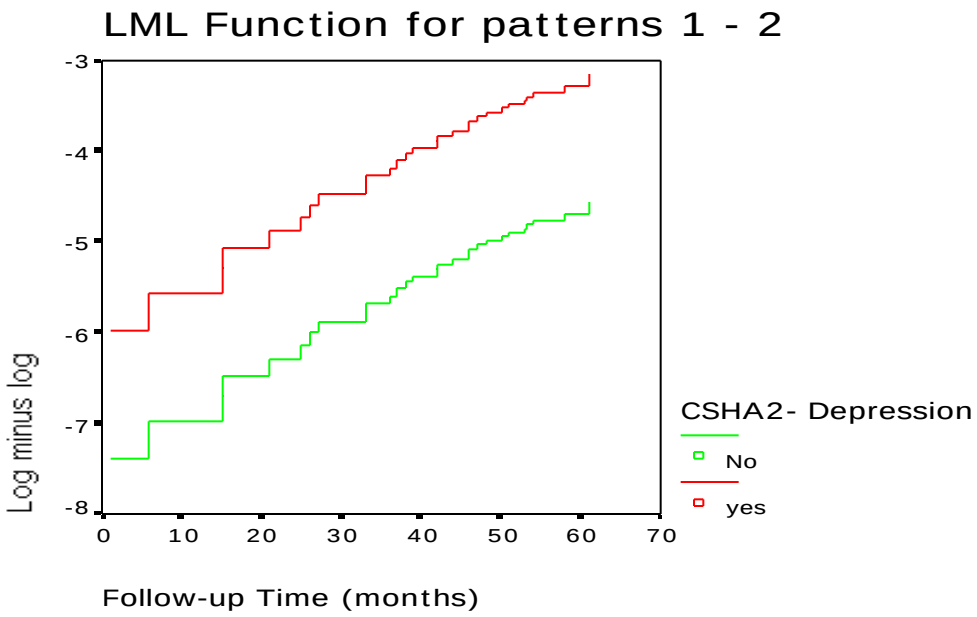
60
70
Follow-up Time (months)
Institutional status
Community
Institution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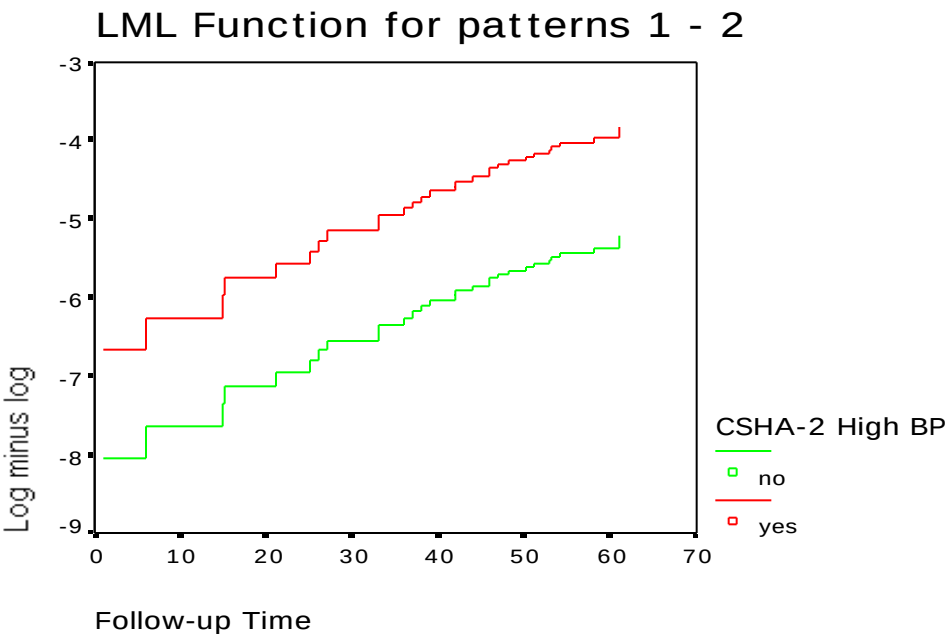
70
Follow-up Time (months)
CSHA2- Depression
No
yes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Log minus log
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10
20
30
40
50
60
70
Follow-up Time
CSHA-2 High BP
no
yes

4.3.9 Vascular Dementia and Age at Onset

4.3.9.1 Linear Regression Model

Using a linear regression model, the effect of HRT on age of VaD onset was assessed. The dependent variable was age at VaD onset. HRT status was not found to significantly predict for age of disease onset when either entered alone or with age in the model (Table 4.34). No other variables entered into the model were found to be significant.

Table 4.34: Final Main Effects Model: Predictors of Age of VaD Onset

Variable (reference)	**β (S.E.)**	**Sig.**	**95% C.I. for Exp (β)** **Lower**	**Upper**
Age-2	1.063 (.055)	.000	.949	1.176
HRT (yes)	-1.001 (1.009)	.331	-3.079	1.078

CHAPTER 5: GENERAL DISCUSSION

1.1 Summary of Results and Discussion

1.1.1 Objective #1: Prevention Bias: Are the characteristics of HRT Users different from Never Users?

Based on the model fitted for HRT status, it is apparent that certain differences exist between the HRT User groups. Certain differences in the characteristics of users as compared to non-users seem almost intuitive. Women in the younger age group may have been exposed to a different social milieu, one more promoting and accepting of medical intervention and hormone use to maintain a woman's youthfulness and health, as compared to their older counterparts. In any case, a greater proportion of hormone users belonged to the youngest age group. As well, women with higher incomes relative to those in the under $20,000 category would financially be more able to afford the cost of monthly hormone supplements, as well as to potentially adopt different health behaviours. Sherwin's healthy-user bias may be evidenced in the fact that women using vitamin E and multi-vitamins were more likely to have used HRT, although it would be interesting to compare other relevant health behaviours. Still this could be viewed as signifying a greater inclination to engage in health-promoting activities. Even the difference according to flu shots may possibly indicate that women in the HRT never user group had a preference for the "natural", although this is speculative and cannot be ascertained from a study of this nature. Finally, certain health conditions may encourage or deter HRT use. Diabetics may be less apt to add HRT to their daily regiments because of drug interaction concerns or just the inconvenience of using another medication. Overall, differences between the characteristics of the two groups exist, which is consistent with the literature (129, 133, 135).

By assessing differences between the HRT user groups, one is able to gain some insight as to whether healthy-user bias could potentially impact study findings. Still, it

is difficult to ascertain whether or not these factors mediate the development of dementia and the manner by which they act. However, it is important that these variations were adjusted for in the modeling strategies for cognitive decline and disease. Unfortunately, it is unlikely that all of the confounding effects can be controlled for, even with a well-designed study. Put another way, it would be improbable that statistical analysis could 'erase' the differential effects that certain lifestyle factors and behaviours confer on the individual. Subtle differences in the lifestyles and behaviours between groups also can have an impact on disease development, particularly since there may be other group distinctions that have been overlooked. Variations, such as found here, may differ in other study populations and must be considered. In terms of the problem of prevention bias, research on HRT and cognition must aim to consistently and adequately control for such differences between HRT user groups that may have an effect on the study's outcomes.

1.1.2 Objective #2: Is there an increased diagnosis of cognitive impairments and dementia in women never using HRT as compared to HRT users?

There was a difference in the distribution of cognitive decline, impairments, and dementia in the ever and never user groups. More HRT never users experienced cognitive decline when compared to HRT users. A greater proportion of HRT never users experienced CIND (11% versus 7%), developed AD (4% versus 2%) and VaD (1% versus .3%) as compared to HRT users. Conversely, a larger portion of HRT users were either diagnosed or screened as normal 90% versus 83%) than HRT never users at follow-up. At first glance then, it appears that the cognitive status of HRT users is superior to the cognition of HRT never users. Notably, these results are descriptive and do not control for the effects of age or other intervening factors.

1.1.3 Objective #3: Is HRT a significant predictor for CLoND, CIND, AD and VaD?

HRT status was not a significant predictor for the CIND and CLoND models, but did predict for AD and VaD. HRT did predict for all- and reduced-cause CIND at certain levels of educational attainment. See table 4.36 for a summary of findings for all outcomes. The findings for each outcome are discussed below.

Table 4.35: HRT Status as a Predictor for All Outcomes (OR, 95% CI)

	Exp (β)	95% CI
All-cause CIND	**1.304**	**0.506 – 3.360**
Reduced-cause CIND	**0.822**	**0.358 – 1.887**
CLoND	**1.148**	**0.717 – 1.839**
AD	**10.134**	**1.301 – 78.946**
VaD	**4.985**	**1.160 – 21.411**

1.1.3.1 All-cause CIND

After controlling for other covariates, HRT status was not found to significantly predict for all-cause CIND (95% CI, 0.506-3.360). Since HRT was found to interact with education and exercise, further analysis was carried out to ascertain the nature of this interaction. It was found that the interaction between the lowest level of education (6 years or less) and HRT status was borderline significant. Therefore, the risk for women with low education who did not use HRT was double the risk for women in the same educational group using HRT. Interestingly, the interaction between HRT status and the 10-12 year educational level was also significant. It was found that women with 10-12 years of schooling who did not use HRT were 4 times more likely than women with similar education who had used HRT to be diagnosed with all-cause CIND. Therefore HRT may theoretically be more beneficial for high-risk individuals such as women with low-level education. However, it is difficult to explain the increased risk in the 10-12 year category and the lack of a trend across different levels of education. It is possible that the interaction between education and HRT has masked at least some of HRT's effect in other studies. Since studies on cognition or dementia generally have not included a discussion of interaction assessment or findings, it is hard to determine if this has been the case in other research. In addition to education, HRT status was also found to interact with family history of AD. A greater proportion of women with a family history of AD have used HRT, and it may be that women with a known predisposition to AD are more inclined to use HRT as a preventative method. However, when looking at the interactional effect for all-cause CIND, no significant differences in risk emerged between the never and ever user groups.

In the literature, the relationship between milder cognitive impairments and HRT has been examined to some degree. Most of this type of research focuses on short-term improvement on cognitive measures in normal women in the relatively younger age groups. Available research has found inconsistent effects of HRT on verbal memory and reasoning, frontal functions and speeded attention (163). Lack of test standardization, absence of a full clinical evaluation, small sample size, and limited inclusion of other covariates are some of the limitations in research up until now and make generalizations difficult. The present study has rectified some of the methodological problems experienced by including a battery of standardized tests, complete clinical evaluation, and assessment of change over a five-year period.

Other predictors for CIND have emerged from the analysis. Age, particularly being over 85 years old, is a strong risk factor for cognitive impairment. Interestingly, lower levels of education, current depression, family history of AD, NSAID use, regular exercise, stroke, and residential status all were significant predictors for all-cause CIND; all these factors have also been identified in the literature as risk factors for dementia.

5.1.3.2 Reduced-cause CIND

As with all-cause CIND, HRT did not appear to achieve statistical significance in this model (95% CI, 0.358-1.887). It was interesting to compare the more inclusive all-cause CIND group to the reduced category, since differences in risk factors may point to distinctive features in the pathology underlying the CIND classification. As well, the reduced-cause CIND group is likely more homogenous than the all-cause group. Given that the HRT-education interaction persisted for both models, education is likely an important modifier of HRT's relationship with cognition.

The finding that HRT status was not a significant predictor for reduced-cause CIND had to be interpreted cautiously due to interaction effects. As with the all-cause CIND model, odds ratios for each level of interaction were calculated. The finding that HRT never users with 10-12 years of education are at an increased risk for reduced-cause CIND as compared to HRT ever users with the same education is puzzling. It was anticipated that this type of interactional effect would be found for the lowest level

of education, which is often implicated as the highest risk category for cognitive decline.

Several predictors changed when the CIND category was reduced in the model. Mental retardation, psychiatric illness, and regular shellfish consumption were factors significant in the all-cause model, but which were no longer significant in the reduced model. In comparing the reduced-model to the all-cause model, theoretically it was thought there would be a difference in terms of HRT's significance as a predictor. The rationale was that by removing some of the causes, the reduced-cause model might be more similar to the dementia pathology. No such difference was observed in HRT status between the two CIND models, however there were variations in which other covariates achieved significance.

5.1.3.3 CLoND

After consideration of many relevant covariates, HRT status was not found to significantly predict for CLoND (95% CI, 0.717-1.839). In this particular model however, it appeared to interact with family history of AD. Further exploration of the interactional effect found that HRT never users with a family history of AD were at a reduced risk for CLoND as compared to HRT users with a similar family history. This finding requires further examination in other study populations given that it may be spurious.

When comparing the CLoND model to the CIND models, depression, education, family history of AD, NSAID use, Parkinson's disease, regular exercise, residential status, and stroke were all similarly significant throughout the models. Marital status, region, and thyroid condition were predictors in the CLoND model, whereas these variables did not reach significance in the CIND models. Women who were divorced or separated were found to be at an increased risk for CLoND. The CLoND classification is largely understudied and is a relatively new and not well-understood concept. This research attempted to use CLoND to gain a better understanding of the nature of cognitive decline as it relates to HRT use. And although there is not a striking association between HRT and CLoND, the use of the pre-clinical cognitive decline categories can helps us to further understand the progression from normal cognition to disease.

5.1.3.4 Alzheimer's Disease

Based on the results of the final main effects model, HRT use appears highly protective for AD. However, the 95% confidence intervals (CI) are quite wide for the variables HRT status, education, and for the 75-84 year age group. The standard error is also large in comparison to the HRT beta-coefficient. A large confidence interval and standard error indicates that the point estimate lacks precision and is unstable. Since there were only 27 participants with AD that reported having used HRT, it may be difficult for the model to consider as many covariates as were entered. Another possible explanation for the wide 95% CI is that there is interaction present between education and HRT. When interaction is assessed, the 95% CI for the levels of the interaction term become more stable. Interaction calculations found that HRT was protective for women with 13 or more years of education, but not for women with other levels of education. When calculating risk for the highest educational category (13 years or more), the limited sample made it difficult to obtain an accurate estimate. Importantly, the fact that fewer AD cases used HRT may strengthen the case for HRT as a protective factor in disease development, but unfortunately it can also present a problem for obtaining accurate and precise estimates. These interaction effects should be examined in future HRT-cognition research.

The model found that HRT status interacts with education. Therefore, further calculations were used to explore the type and strength of this interaction. It was found that HRT never users in women with high education (13 years or more) were over ten times more likely to develop AD than HRT users in the same education category. It is difficult to know if this is a spurious finding or if women not using HRT with higher educational levels are at increased risk for dementia as compared to women with a similar educational background who use HRT. In general, persons with higher education are at the lowest risk for AD, hence even a ten-fold increase may not be clinically remarkable.

It is difficult to explain these results when considering the variation in study findings to date. In the literature reviewed, six of the ten studies revealed a protective association between HRT and Alzheimer's disease. However, these were all observational research. The only long-term RCT, which was recently carried out by the

WHI-MS, found HRT to increase a woman's risk for dementia (VaD and AD combined) (47). A notable limitation of this study was that HRT was administered to women 65 and older, and although these women may have used HRT previously, the duration of lifetime HRT use was not considered. Non-adherence was a problem in this study as well, with 52% of the sample stopping treatment at some point during the trial. Finally, many of the participants developed dementia after becoming non-adherent. Hence, even though RCTs are the gold standard in epidemiology, there are limitations with the WHI-MS.

There is evidence to suggest that estrogen is the mechanism activating the cognitive benefits of hormone therapy. It is also believed that certain forms of progestins may actually wash out estrogen's benefits. In one study it was found that medroxyprogesterone acetate, a common progestin, blocked estrogen-induced beneficial effects (132). Therefore ERT may be more effective than HRT, with combination therapy actually being unproductive altogether. With a large portion of women known to use ERT in this current study's sample (70%), the findings are consistent with this hypothesis. The age group of the sample increases the likelihood that estrogen-only preparations were used, at least initially, since ERT was the primary hormone therapy used up until 1975, at which time estrogen-only preparations were found to increase risk for endometrial cancer (164). Another sub-component of the WHI-MS is examining estrogen-only preparations and its affect on dementia; this will help to decipher the complex connection between type of hormone preparation and cognitive decline.

5.1.3.5 Vascular Dementia

According to the results of the VaD model, HRT never users are at a significantly increased risk for disease. Notably, the effect size for HRT status was quite sizeable; the 95% confidence interval wide; and arguably, the standard error high. This is undoubtedly due to the small number of VaD cases. There were only three VaD cases that had used HRT and the remaining 26 participants who developed the disease had never used HRT. This makes it very difficult to ascertain a precise point estimate with a narrower confidence interval. Furthermore, if the sample size had been larger, other relevant predictors and interaction terms may have emerged that did not reach

significance in this particular model. The decision to collapse education into two categories (6 years or less, 7 years or more), when all other models were constructed using four, was necessary because of the small numbers. As discussed previously, the lower levels of educational attainment have been found to exact the highest degree of risk and this reclassification of education retained the ability to observe this effect. Age is preferably used as a categorical variable since it is easier to see its marked effect when collapsed. As a continuous variable in this model, age can be seen to have a small but significant effect each year that one ages.

Research examining HRT's effect on VaD is limited. The only known study including VaD in analysis is the WHI-MS study and it appeared to be protective. However, the WHI-MS research paper considered AD and VaD cases in combination, which makes it impossible to decipher HRT's effects on outcomes individually. Nonetheless, evidence suggests that HRT has vascular benefits(55, 66), which is consistent with HRT as a protective factor for the VaD pathology.

1.1.4 Objective #4: Is the age of onset of dementia later in women having used HRT than in women never having used HRT?

There are still questions regarding the nature of HRT's protective effect on cognition. Does HRT prevent the development of dementia or simply delay its clinical onset? Using linear regression with age of dementia onset as the outcome variable, the two HRT groups were compared and assessed for differences in timing of AD and VaD onset. A linear regression model was fit using age of dementia onset as the outcome. Analysis found that after controlling for the participants' age, there was no statistical association between age of AD onset and HRT use ($p=0.628$). Similarly, there was no significant relationship identified between age of VaD onset and HRT status ($p=0.331$). Notably, factors affecting dementia's clinical onset are not fully understood. That is, it is unclear how much damage must occur in the brain prior to symptom presentation and what factors accelerate or decelerate this process; and if the threshold varies for different people. It is known that the APOE-4 allele is predictive of dementia timing, however this information was not available for analysis.

1.1.5 Objective #5: Is there a dose-response relationship between HRT usage and CIND, CLoND, AD and VaD?

Because some studies have shown length of hormone use to be clinically important in terms of dementia risk (96, 97, 102, 105), HRT status was broken into categories according to duration of use. HRT duration was initially tested using finer categories and then collapsed more broadly. Both variables were tested in the all-cause CIND, reduced-cause CIND, CLoND, and AD models, but did not reach significance. Interestingly, HRT duration was not significant (p=.257) in the AD model, however, there was a trend for use less than five years to be protective, whereas use longer than 5 years and no use at all confer similar risk. The effect of HRT duration could not be assessed in the VaD model due to small sample size. Information on the dose prescribed to each woman was not collected during the CSHA, and therefore this thesis was unable to look at the effect of dose.

1.2 Study Strengths

The strengths of the CSHA lie with its large sample size, longitudinal and case-control study design, inclusion of community and institution populations, and the determination of cognitive status by trained clinicians using standardized measures and diagnostic criteria. In terms of the thesis study design, the use of incident cases; comprehensive inclusion of covariates, confounders, and effect modifiers; thorough assessment of prevention bias; inclusion of a spectrum of cognitive states; consideration of HRT's durational effect and impact on age of disease onset all served to strengthen the study conclusions and remedy the methodological issues plaguing HRT research. In an effort to discern the nature and strength of the association between HRT and cognition great care was taken to include all necessary risk and confounding factors, using appropriate statistical modeling strategies and interaction assessment.

Although this sample included older women who are at higher risk for dementia-related illness and cognitive decline, HRT use was considered at the time when it was likely most effective. The recent WHI-MS randomized women ages 65 and older to HRT, a time when hormones may have a more limited effect since dementia risk rises dramatically after age 65 indicating that the pathology is already in progress. The WHI-MS study may have essentially been assessing HRT's efficacy as a treatment, rather

than as a preventive method. Whereas by using data that describes HRT exposure over past decades, we are able to capture a more accurate picture of hormone supplementation as a preventive technique.

1.3 Study Limitations

With any research work, there are certain to be limitations. It is the type and nature of these limitations that is key in validating the study's findings.

1.3.1 Exposure Measurement

The results of the statistical analysis are only as good as the quality of data used to estimate the effects. Fortunately, the data collected during the CSHA was comprehensive and quality was an important consideration. However, a cohort study by nature presents unique challenges in terms of accurately capturing an individual's exposure history. Furthermore, missing data is a reality – information missed by interviewers or by participants in the mail-out questionnaire and individuals unsure or unwilling to disclose.

Validity is the extent to which a particular indicator measures what it is supposed to measure. Clearly, validity is an important issue in the data collection process. When requesting information from participants or proxy respondents, certain questions required a summative answer. For instance, the question "have you ever drank wine regularly (at least once/week)" appeared on the baseline risk factor questionnaire. Here those responding 'yes' were likely not a homogenous group, in that there will be range with some drinking wine each day for years and others once per week for a shorter period of time; nonetheless each would have responded 'yes'. The impact of these generalizations cannot be easily assessed, since some exposures may have an important effect whether used often or intermittently. Moreover, it may be impractical to ask participants for an exact value, particularly if one is inquiring about long periods of time, as was the case here.

Finally, certain information was not obtained at any of the three study phases, while some data was only asked of the clinical sample. APOE genotype was an important and notable limitation. APOE-4 is a definite and important risk factor for dementia and cognitive impairments. APOE status was assessed through a blood

sample for the nested case-control sample during the CSHA, and despite our initial intention to include the variable APOE, not enough data was available to comfortably carry out analysis using this smaller sub-sample. APOE and HRT use may interact, with women carrying the APOE-4 allele(s) benefiting more from HRT use. Consideration of this interaction is suggested for future HRT-dementia research. Variables such as hysterectomy status, age at menopause, and use of phytoestrogens may have provided an important picture of lifelong estrogen exposure, however were not available for analysis.

1.3.2 Bias

Out of all observational study designs, the prospective cohort study is the strongest (131). In comparison to case-control and cross-sectional studies, it provides the more compelling case for causation. Nonetheless, it is not without limitations. Selection bias, loss to follow-up, and surveillance bias are some of the problems encountered with cohort studies.

5.3.2.1 Selection Bias

Selection bias results when the probability of the event of interest occurring is strongly related to how the sample was obtained (131). In cohort studies, selection bias is most likely to occur due to lost-to-follow-up. Since the baseline CSHA sample did include dementia cases, selection bias could have possibly been introduced. This would have occurred when a participant refused to participate in a phase of the study due to ill health or cognitive problems, which may include the outcome of interest or dementia. This particular study required that the sample was cognitively normal in 1991 and therefore minimizes the risk of initial selection bias.

Overall, the CSHA sampling design was population-based and representative (165). However, it is still possible that individuals choosing not to participate could have introduced bias. A study looking at the correlates of nonparticipation in the initial CSHA sample found that older age, female sex, and living in a large city (>1 million) were all significantly related to refusal status (166). Aside from a slightly higher proportion of high school graduates in the CSHA (45% vs 36%), the demographics of its baseline sample closely approximated the 1991 Census (165).

5.3.2.2 Loss to Follow-up

By nature, cohort studies will tend to lose a number of participants due to a wide range of reasons. Dementia increases mortality risk, therefore participants who died between study phases may have developed dementia without the CSHA knowing. As a result, cause of death information was obtained for all participants dying between and during study phases. From a decedent interview and death certificate, an algorithm was used to determine cognitive status at the time of death. Because people who died before CSHA-2 were not questioned about their HRT status, this thesis work was not able to include this decedent information as a proxy diagnosis, but instead this group was removed from the sample. Therefore, these incident dementia cases presenting between CSHA-1 and –2 would therefore be missed. It is possible then that this has resulted in a 'survival sample', where the participants are healthier than those lost to follow-up. The concern is that women who did not participate at follow-up were different from women who remained in this study. Moreover, if HRT does confer a survival benefit (136), then women in this sample not using HRT may be hardier than other HRT users, which may have lead to underestimation of HRT's effects.

5.3.2.3 Surveillance Bias

Surveillance bias occurs when one group is studied more closely than the other (131). In this way, more exposures or conditions may be found in one group when they are equally present in the other. This could happen with both the outcomes and exposures. Because all participants were screened in the same manner and followed a very similar diagnostic protocol, it is less likely this would have occurred biasing the outcome. Although exposure information may have been more complete for those attending a clinical assessment, particularly since both an informant interview and a clinician's history were completed for each participant.

5.3.2.4 Information Bias

Two forms of information bias are recall and misclassification bias. Both are recognized limitations to this present study and must be considered when interpreting the findings.

Some variables within the CSHA dataset were collected prospectively, while others required participants to recall past illness and exposure. An inherent risk in the

latter approach is introducing recall bias. HRT status was obtained by asking women to recall past and present use of HRT. Information recalled years or even decades prior is likely to be imperfect. It is difficult to know if certain women were systematically under-reporting exposure while other women were over-reporting exposure. As mentioned previously, information on the type of hormone therapy utilized was omitted from analysis because of large amounts of missing and vague (eg. "hormones") data. Because information on the type of HRT was not complete and therefore was not considered in analysis, the results are not specific to one preparation or another. Notably, most HRT users (70%) reported taking ERT and this is consistent with the more prevalent use of estrogen-only preparations in decades prior. Interestingly, it is more likely that participants would have forgotten an exposure than to have fabricated information (131). Hence, one might postulate that women reporting HRT use would be supplying fairly accurate information. Intuitively, one might suspect that if women reported 'never use', this would be either correct or their use of HRT was for a limited duration. Some studies have used prescription databases to crosscheck participants' reports of HRT use. This was beyond the scope of this thesis study and therefore we were unable to verify HRT self- and proxy-reported information.

Misclassification bias can occur either by misclassifying exposures, disease, or both. Differential misclassification is a potential concern in this study. This happens when the frequency of under-reporting is different for cases or controls. Since time-2 information for participants with dementia was obtained from a proxy respondent, it is possible that the proxy's data would be less accurate than if given by the participant herself. That is, the proxy may not have been aware of HRT use. Encouragingly, when kappa values were run for HRT status, where cognitively normal participants and their proxy respondents answered the HRT question, the kappa agreement was quite high (kappa=.801). This means that there was a high level of correlation between the two responses, and may indicate that proxy respondents supply quite accurate history on medication usage.

Regrettably, kappa values were not strong for all exposures. As one might expect, proxy respondents seemed to be less aware of certain exposures or health conditions. For instance, the variables for occupational exposures to glues, pesticides

and solvents had low kappa agreement; as did the variables for diptheria, polio and tetanus shots. This is likely due to the fact that these exposures would have occurred earlier in the participants' life making proxies less aware of them. The quality of the data then may affected the inclusion of the variables in the final models; that is, occupational exposures cannot be ruled out as risk factors, and the association between tetanus shots and cognitive status requires further investigation. When the kappa values were low, one would expect that the data collected from the participants were of higher quality, which means data for participants with dementia would be less accurate than for the cognitively normal participants.

5.3.2.5 Statistical Power

Statistical power determines the maximum effect size detectable by the study. Here statistical power was quite low for the outcome of VaD. This was a result of the minimal number of incident cases at follow-up and was unavoidable. Small sample size very likely limited the ability to control for interactions and to identify other relevant covariates. However, the model indicated that HRT was a strong predictor of VaD and therefore HRT status was found to be a significant risk factor. Since the effect size was quite large for HRT, low statistical power did not appear to be an important concern.

5.4 Implications for Future Research

It is not prudent to treat HRT users as one homogenous group, nor it is safe to assume that one preparation is equivalent to another. Future research would be wise to focus on the type of hormone therapy – estrogen-only versus estrogen-progestin combinations – separately and to specify the means of administration (eg. pill, patch, cream). Although the current study did not find a significant duration effect, it is very likely that the length of HRT use impacts both positive and negative health outcomes. Interestingly, research indicates that use of HRT greater than five years increases HRT users' risk for breast cancer (30), and similarly we found a trend for HRT to have a greater cognitive benefit when used for less than five years. Future research should ensure that study samples include adequate numbers for each level of duration in order to adequately examine the effect of length of use. Finally, an interesting and potentially valuable interaction may exist between HRT use and APOE status. That is, women at

increased risk due to APOE-4 genotype may benefit more from HRT use than those not having an E4 allele(s). Unfortunately, we were not able to assess this interaction due to sample size limitations for participants having APOE information. Additional studies may want to use datasets where APOE status is available in adequate numbers in order to investigate this potential interaction effect. As with research in general, the importance of good quality study designs and the inclusion of relevant risk and confounding factors cannot be overstated. In the case of HRT research, conflicting results have led to considerable confusion in terms of what the risks and benefits of HRT truly are.

5.5 Implications for Women: The Decision to Use HRT or Not

Understanding the relationship between HRT and cognitive decline is highly relevant to clinicians and women in general. Doctors and researchers need to know if HRT, in fact, does have a protective effect on cognition and if this effect is clinically significant. A February poll commissioned by Eli Lilly Canada in 2003 found that forty-four per cent of women using hormone replacement therapy have stopped taking it in the past year, and another 32 per cent say they will discontinue it in the coming months (167). This is likely the result of the recent flood of negative and discouraging research indicating HRT users are at an increased risk for a variety of serious illnesses and this cannot or should not be overlooked. Therefore the results of the present study must be put into context. The protective effect found for dementia-related diseases should not take precedence over other negative and serious illness-inducing effects. Klein & Dumble (1994) put forth a portrayal of the demoralizing effects that HRT as a treatment for menopause may have on women and the confusion that may accompany the choice to use HRT (168).

> "Rigid in their 'happy' state, heterosexually active because they must, running from mammography to bone density test to endometrial biopsy, coping with migraines, hypertension, and weight gain; stressed out from surviving the cancer scare which resulted in a breast biopsy --- all from a drug prevention of osteoporosis and heart attacks which they may never get? It is, we suggest, real live midlife women – albeit so far mainly western middle-class women – who today are pressured to feel guilty even if they don't go on HRT and often still feel guilty if they do." (p.339-40).

The same can be said for dementia. While identifying the cognitive advantages of HRT is an essential element of each woman's risk-benefit considerations, there is presently no accurate way to predict which women are at risk for dementia at the time of menopause, when HRT use is likely most effective. Consequently, many women would be unnecessarily relying on HRT for the prevention of a disease they may never develop. Furthermore, it is important to consider if the cognitive benefits override the other potentially harmful adverse effects. Until the time where we are able to more accurately discern which women would receive the greatest benefits from HRT supplementation, we run the risk of coercing all women – regardless of necessity – to use a therapy that is unsafe for certain sub-groups and questionably effective. We may also further the notion that menopause is an illness and potentially affect how women view this phase of their lives.

On the other hand, if estrogen, which seemed to be the predominantly used preparation in this study, is protective against cognitive decline then this knowledge cannot be dismissed either. It may be that there are certain routes of hormones administration that are more beneficial, with fewer side effects. For instance, non-systemic forms of progesterone have been found to benefit some women without having to travel throughout their bodies, thus minimizing negative side effects such as increased risk of breast cancer, but still countering the increased risk of endometrial cancer. As well, the FDA recently approved a lower-dose version of combination HRT therapy (169). Prempro™, made by Wyeth Pharmaceuticals, was revised probably with the hope of decreasing the risk for negative long- and short-term outcomes. The new lower-dose appears to be just as effective as the higher, more commonly prescribed dosage for the reduction of menopausal symptoms such as hot flashes (170). It is yet to be seen if lower-doses of HRT will qualitatively improve the viability of HRT as a treatment of women's menopausal concerns, or if this old-made-new technology is very much similar to the currently used preparations. Based on one clinical trial showing HRT to be relatively unsafe and ineffective for the prevention of dementias, we cannot close the book on hormone supplementation. But neither can we mass prescribe a substance that may only be appropriate and pertinent to certain sub-groups of women.

The role of physicians in society is unquestionably powerful. This reality must be seriously considered when counseling individual women on the use of HRT, and physicians must be responsible to keep up-to-date on current research and the hormone controversies. This will be the only way that practitioners can give adequate counseling to their female patients on a case-by-case basis. In the end, each woman will decide for herself if HRT is the necessary and appropriate intervention for her menopausal concerns. Therefore it is imperative that women are armed with quality evidence and thereby given a clearer and fuller picture to aid in this complex, obscure, and highly personal decision.

Prevention bias can teach us a good deal in terms of the maintenance and enhancement of women's health as they age. Women using HRT appeared to have some characteristics, behaviours, and health profiles that likely confer benefits beyond our ability to control. However, these differences may equally contribute to wellness over-and-above the use of hormone supplements. Therefore one must be cautious in contributing HRT use solely to the cognitive benefits observed, when in fact, a lifetime of lifestyle decisions, behaviours, and environments doubtlessly play a significant role in determining cognitive status and the overall health of women as they age. It may be that an exclusive focus on medical intervention is shortsighted, when a concentration on lifestyle modification and healthy living would be more fruitful.

HRT has been confirmed here as a protective factor in the development of AD and VaD and this cannot be disregarded. Considering the sizeable increase in the number of dementia sufferers expected in future years, the economic and social cost of care provision, and the burden placed on the health care system, a genuine risk reduction would be of tremendous public health importance (19). In terms of using HRT as a prevention technique, future research would do well to focus on a means of administering estrogen in a safer manner. Mounting dementia research will help to identify women at the greatest risk for disease, with certain portions of the female population being more likely to require medical intervention to maintain normal cognitive functioning. Unquestionably, identifying the cognitive advantages of HRT is an essential element of each woman's risk-benefit considerations in terms of hormone use after menopause, but still it remains only one piece of the puzzle.

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APPENDIX A

Ethics Approval

For ethics form

APPENDIX B

Breakdown of Variables According to Data Source

Heart Attack-1		2423 (72)	234 (7)		68 (2)			103 (3)	117 (3)	
Diabetes-1		2185 (65)	236 (7)	936 (28)		27 (1)				
Diabetes-2							3029 (90)		348 (10)	
Stroke-1		2095 (62)	230 (7)	1015 (30)		42 (1)				
Stroke-2							3156 (93)	21 (1)	194 (6)	
High Blood Pressure-1		2377 (62)	226 (7)	739 (22)		41 (1)				
High Blood Pressure-2										
Parkinson's disease-1		2135 (63)	239 (7)	985 (29)	23 (1)					
Parkinson's disease-2							3163 (93)		188 (5)	
Thyroid Condition		2241 (66)	234 (7)			93 (3)			769 (23)	
Arthritis		2431 (72)	216 (6)	708 (21)						
Kidney Disease		2161 (64)	232 (7)	962 (28)						
Epilepsy		2137 (63)	236 (7)			74 (2)			245 (7)	
Self/ Proxy Reported Depression-1		2151 (64)	251 (7)			58 (2)				
Self/ Proxy Reported Depression-2							2067 (61)		1065 (31)	
Other Psychiatric Illness		2079 (61)	267 (8)	975 (29)	58 (2)					
Age	3384 (100)									
Education	3371 (100)									
Income							2267 (67)	332 (10)		164 (5)
Marital Status-1		2757 (81)	229 (7)	374 (11)	22 (1)					
Marital Status-2							3205 (95)	174 (5)		

Smoking Status		2670 (79)	238 (7)		31 (1)			134 (4)		
Regular Spirit Drinking		2671 (79)	213 (6)							
Regular Wine Drinking		2665 (79)	215 (6)							
Regular Coffee Drinking		2721 (80)	227 (7)							
Regular Tea Drinking		2715 (80)	223 (7)							
Regular Shellfish Consumption		2673 (79)	218 (6)							
Regular Exercise		2688 (79)	230 (7)							
Regular use of Painkillers		2640 (78)	185 (5)							
HRT Use							2364 (70)		1020 (30)	
APOE									707	
Family History of AD		2400 (71)	207 (6)					407 (12)		
Family History of Senile Dementia		2469 (73)	231 (7)		23 (1)					
Family History of Mongolism		2364 (70)	232 (7)							
Family History of Mental Retardation		2350 (69)	230 (7)							
Exposure to Glues		2445 (72)	239 (7)							
Exposure to Solvents		2480 (73)	203 (6)							
Exposure to Pesticides		2479 (73)	206 (6)							
Flu shot		2600 (77)	220 (7)							
Polio shot		2516 (74)	218 (7)							
Diptheria shot		2485 (73)	220 (7)							
Tetanus shot		2518 (74)	218 (7)							
Head Injury		2517 (74)	217 (7)			69 (2)			158 (5)	

APPENDIX C

Bivariate Tables

BIVARIATE ANALYSIS: HRT USERS COMPARED TO HRT NEVER USERS

Variable		HRT Users (n=909)	HRT Never Users (n=2475)	p-value
Health Conditions				
Heart Attack-1	Yes No	51 (6) 678 (75) *180 (20)	177 (7) 1804 (73) *494 (20)	**.107**
Other Heart Condition-1	Yes No	171 (19) 508 (56) *230 (25)	376 (15) 1362 (55) *737 (30)	**.061**
Diabetes-1	Yes No	76 (8) 833 (92) *0	232 (9) 2243 (91) *0	.364
Diabetes-2	Yes No	90 (10) 817 (90) *2 (0)	326 (13) 2144 (87) *5 (0)	**.010**
Stroke-1	Yes No	40 (4) 868 (95) *1 (0)	94 (4) 2380 (96) *1 (0)	.424
Stroke-2	Yes No	73 (8) 833 (92) *1 (0)	202 (8) 2263 (91) *10 (0)	.897
High Blood Pressure-1	Yes No	366 (40) 543 (60) *0	989 (40) 1485 (60) *1 (0)	.879
High Blood Pressure-2	Yes No	415 (46) 493 (54) *1 (0)	1085 (44) 1381 (56) *9 (0)	.376
Parkinson's disease-1	Yes No	9 (1) 899 (99) *1 (0)	25 (1) 2449 () *1 (0)	.960
Parkinson's disease-2	Yes No	18 (2) 885 (97) 6 (1)	57 (2) 2407 (97) 1 (0)	.577
Thyroid disease-1	Yes No	188 (21) 566 (62) *155 (17)	371 (15) 1662 (67) *442 (18)	**.000**
Arthritis-1	Yes No	608 (67) 295 (32) *6 (1)	1514 (61) 938 (38) *23 (1)	**.003**
Kidney disease-1	Yes No	132 (15) 771 (85) *6 (1)	242 (10) 2210 (89) *23 (1)	**.000**
Epilepsy-1	Yes No	5 (1) 722 (79) *182 (20)	26 (1) 1939 (78) *510 (21)	**.170**
Self or Proxy Reported Depression-1	Yes No	124 (14) 570 (63) *215 (24)	251 (10) 1515 (61) *709 (29)	**.023**
Self or Proxy Reported Depression-2	Yes No	114 (13) 726 (80) 69 (8)	277 (11) 2015 (81) 183 (7)	.265
Other Psychiatric Illness-1	Yes No	227 (25) 681 (75) *1 (0)	538 (22) 1933 (78) *4 (0)	**.047**

Demographic Information				
Age-1	65 to 74 yrs 75 to 84 yrs 85 yrs & over	594 (64) 279 (31) 36 (4) *0 (0)	1061 (43) 1117 (45) 297 (12) *0 (0)	**.000**
Age-2	65 to 74 yrs 75 to 84 yrs 85 yrs & over	355 (39) 451 (50) 103 (11) *0 (0)	568 (23) 1236 (50) 671 (27) *0 (0)	**.000**
Marital Status-1	Currently / Common Law Divorced/ Separated Widowed Never	425 (47) 48 (5) 365 (40) 71 (8) *0	869 (35) 93 (4) 1277 (52) 234 (9) *2 (0)	**.000**
Marital Status-2	Currently / Common Law Divorced/ Separated Widowed Never	331 (36) 48 (5) 459 (50) 70 (8) *1 (0)	634 (26) 76 (3) 1524 (62) 237 (10) *4 (0)	**.000**
Education	6 yrs & under 7 – 9 yrs 10 –12 yrs 13 + yrs	100 (11) 222 (24) 342 (38) 243 (27) *2 (0)	309 (12) 687 (28) 889 (36) 579 (23) *11 (0)	**.057**
Income-2	< $19,999 $20,000- 34,999 $35,000- 49,999 $50,000 and over	369 (41) 233 (26) 105 (12) 75 (8) *127 (14)	1181 (48) 485 (20) 190 (8) 128 (5) *491 (20)	**.000**
Rural/Urban	Rural Urban	80 (9) 827 (91) *2 (0)	273 (11) 2196 (89) *6 (0)	**.060**
Region-1	Atlantic Quebec Ontario Prairies B.C.	136 (15) 223 (25) 160 (18) 203 (22) 187 (21)	513 (21) 488 (20) 491 (20) 541 (22) 442 (18)	**.000**
Region-2	Atlantic Quebec Ontario Prairies B.C.	135 (15) 223 (25) 163 (18) 200 (22) 188 (21)	513 (21) 485 (20) 494 (20) 539 (22) 444 (18)	**.000**
Residential Status-1	Institution Community	18 (2) 891 (98) *0 (0)	91 (4) 2384 (96) *0 (0)	**.013**

Residential Status-2	Institution Community	43 (5) 866 (95) *0 (0)	258 (10) 2217 (90) *0 (0)	**.000**
Lifestyle Factors				
Regular Smoker	Yes No	343 (38) 503 (55) *63 (7)	744 (30) 1484 (60) *247 (10)	**.000**
Regular Spirit Drinking	Yes No	182 (20) 631 (69) *96 (11)	315 (13) 1767 (71) *393 (16)	**.000**
Regular Wine Drinking	Yes No	139 (15) 679 (75) *91 (10)	265 (11) 1807 (73) *403 (16)	**.003**
Regular Coffee drinking	Yes No	608 (67) 214 (24) *87 (10)	1446 (58) 679 (27) *350 (14)	**.002**
Regular Tea drinking	Yes No	600 (66) 222 (24) *87 (10)	1553 (63) 563 (23) *359 (15)	.826
Regular Shellfish Consumption	Yes No	183 (20) 628 (69) *98 (11)	423 (17) 1658 (67) *394 (16)	**.184**
Regular exercise	Yes No	557 (61) 257 (28) *95 (10)	1327 (54) 777 (31) *371 (15)	**.007**
Vitamin E	Yes No	96 (11) 739 (81) *74 (8)	119 (5) 2051 (83) *305 (12)	**.000**
Vitamin C	Yes No	86 (10) 749(82) *74 (8)	114 (5) 2056 (83) *305 (12)	**.000**
Vitamin B	Yes No	37 (4) 798 (88) *74 (81)	78 (3) 2092 (85) *305 (12)	.284
Multi-vitamin	Yes No	194 (21) 641 (71) *74 (8)	334 (13) 1836 (74) *305 (12)	**.000**
Medication Usage				
Regular Painkiller Use	Yes No	453 (50) 363 (40) *93 (10)	1059 (43) 1003 (41) *413 (17)	**.039**
Statins	Yes No	26 (3) 809 (89) *74 (8)	42 (2) 2128 (86) *305 (12)	**.052**

Other Exposures				
Past Head Injury	Yes No	115 (13) 680 (75) *114 (13)	285 (12) 1867 (75) *323 (13)	.440
Occupational Exposure to Glues	Yes No	67 (7) 695 (76) *147 (16)	154 (6) 1768 (71) *553 (22)	.507
Occupational Exposure to Solvents	Yes No	52 (6) 714 (79) *143 (16)	143 (6) 1774 (72) *558 (23)	.545
Occupational Exposure to Pesticides	Yes No	56 (6) 710 (78) *143 (16)	143 (6) 1776 (72) *556 (22)	.900

Influenza Shot	Yes No	470 (52) 326 (36) *113 (12)	1084 (44) 940 (38) *451 (18)	**.008**
Polio Shot	Yes No	224 (25) 535 (59) *150 (17)	459 (19) 1516 (61) *500 (20)	**.001**
Diptheria Shot	Yes No	196 (22) 550 (61) *163 (18)	413 (17) 1546 (62) *516 (21)	**.004**
Tetanus Shot	Yes No	275 (30) 489 (54) *145 (16)	503 (20) 1469 (59) *503 (20)	**.000**

*missing data

BIVARIATE ANALYSIS: CLOND VERSUS COGNITIVELY NORMAL

Variable			Cognitively Normal-2 (n=2686)	CLoND (n=235)	P-value
Health Conditions					
Heart Attack-1		Yes No	171 (6) 1881 (70) *634 (24)	24 (10) 206 (88) *5 (2)	.280
Diabetes-1		Yes No	236 (9) 2450 (91) *0	23 (10) 212 (90) *0	.605
Diabetes-2		Yes No	323 (12) 2359 (88) *6 (0)	33 (14) 202 (86) *0	**.**369
Stroke-1		Yes No	79 (3) 2605 (97) *2 **(**0)	22 (9) 213 (91) *0	**.000**
Stroke-2		Yes No	160 (6) 2515 (94) *11 (0)	47 (20) 187 (80) *1 (0)	**.000**
High Blood Pressure-1		Yes No	1067 (40) 1619 (60) *0	104 (44) 131 (56) *0	**.174**
High Blood Pressure-2		Yes No	1161 (43) 1515 (56) *10 (0)	120 (51) 115 (49) *0	**.023**
Parkinson's disease-1		Yes No	14 (1) 2670 (99) *2 **(**0)	6 (3) 229 (97) *0	**.000**
Parkinson's disease-2		Yes No	49 (2) 2621 (98) *16 (1)	10 (4) 225 (96) *0	**.012**
Thyroid Condition-1		Yes No	455 (17) 1633 (61) *598 (22)	27 (11) 198 (84) *10 (4)	**.001**
Arthritis-1		Yes No	1683 (63) 995 (37) *8 (0)	148 (63) 81 (34) *6 (3)	**.592**
Kidney Disease-1		Yes No	288 (11) 2387 (89) *11 (0)	39 (17) 190 (81) *6 (3)	**.004**
Epilepsy-1		Yes No	17 (1) 2009 (89) *11 (0)	3 (1) 232 (99) *0	.498
Self or Proxy Reported Depression-1		Yes No	259 (10) 1693 (63) *734 (27)	34 (14) 138 (59) *63 (27)	**.018**
Self or Proxy Reported Depression-2		Yes No	241 (9) 2219 (83) *226 (8)	53 (23 182 (77) *0	**.000**
Other Psychiatric Illness		Yes No	544 (20) 2139 (80) *5 (0)	72 (31) 161 (69) *2 (1)	**.000**
Demographic Information					
Age-1	65-74 75-84 85 & over		857 (32) 1403 (52) 426 (16) *0	17 (7) 106 (45) 112 (48) *0	**.000**

Age-2	65-74 75-84 85 & over	1492 (56) 1042 (39) 152 (6) *0	55 (23) 125 (53) 55 (23) *0	**.000**
Marital Status-1	Currently/ Common Law Separated/ Divorced Widowed Never	1125 (42) 115 (4) 1203 (45) 241 (9) *2 (0)	55 (23) 14 (6) 147 (63) 19 (8) *0	**.000**
Marital Status-2	Currently/ Common Law Separated/ Divorced Widowed Never	856 (32) 101 (4) 1482 (55) 242 (9) *5 (0)	37 (16) 12 (5) 167 (71) 19 (8) *0	**.000**
Education	6 yrs & under 7-9 yrs 10-12 yrs 13 + yrs	245 (9) 699 (26) 1016 (38) 717 (27) *9 (0)	66 (28) 59 (25) 75 (32) 34 (15) *1 (0)	**.000**
Income	<$19,999 $20,000- 34,999 $35,000- 49,999 $50,000 +	1161 (43) 646 (24) 271 (10) 189 (7) *419 (16)	136 (58) 31 (13) 12 (5) 2 (1) *54 (23)	**.000**
Rural/ Urban	Rural Urban	273 (10) 2409 (90) *6 (0)	26 (11) 208 (89) *1 (0)	.652
Region-1	Atlantic Quebec Ontario Prairies B.C.	486 (18) 532 (20) 529 (20) 606 (23) 533 (20)	30 (13) 86 (37) 57 (24) 34 (15) 28 (12)	**.000**
Region-2	Atlantic Quebec Ontario Prairies B.C.	484 (18) 530 (20) 523 (20) 603 (22) 536 (20) *0	30 (13) 85 (37) 58 (25) 34 (15) 28 (12) *0	**.000**
Residential Status-1	Institution Community	38 (1) 2648 (99) *0	22 (9) 213 (91) *0	**.000**
Residential Status-2	Institution Community	105 (4) 2581 (96) *0	46 (20) 189 (80) *0	**.000**
Lifestyle Factors				
Smoking Status	Yes No	905 (34) 1493 (56) *288 (11)	62 (27) 171 (73) *2 (1)	**.001**
Regular Spirit Drinking	Yes No	426 (16) 1917 (71) *343 (13)	24 (10) 176 (75) *35 (15)	**.028**

Regular Wine Drinking	Yes No	354 (13) 1984 (74) *348 (13)	21 (9) 181 (77) *33 (14)	**.068**
Regular Coffee Drinking	Yes No	1707 (64) 674 (25) *305 (11)	144 (61) 61 (26) *30 (13)	.659
Regular Tea Drinking	Yes No	1721 (64) 657 (24) *308 (11)	147 (63) 54 (23) *34 (14)	.816
Regular Shellfish Consumption	Yes No	524 (20) 1825 (68) *337 (13)	24 (10) 172 (73) *39 (17)	**.001**
Vitamin E	Yes No	198 (7) 2226 (83) *262 (10)	6 (3) 200 (85) *29 (12)	**.007**
Vitamin C	Yes No	180 (7) 2244 (84) *262 (10)	9 (4) 197 (84) *29 (12)	**.103**
Vitamin B	Yes No	99 (4) 2325 (87) *262 (10)	8 (4) 198 (84) *29 (12)	.889
Multi-vitamin	Yes No	455 (17) 1969 (73) *262 (10)	30 (13) 176 (75) *29 (12)	**.135**
Regular Exercise	Yes No	1602 (60) 754 (28) *330 (12)	95 (40) 104 (44) *36 (15)	**.000**
Head Injury	Yes No	326 (12) 1957 (73) *403 (15)	37 (16) 196 (83) *2 (1)	.543
Medication Usage				
HRT Use	Ever Never	787 (29) 1899 (71) *0	50 (21) 185 (79) *0	**.009**
HRT Duration	<12 mths 13 mths – 5 yrs 61 mths – 10 yrs >121 mths			**.086**
Age at First HRT Use	40 yrs & under 41-50 yrs 51 – 60 yrs 60 yrs & over			.574
NSAID Use	Yes No	492 (18) 1852 (69) *342 (13)	30 (13) 158 (67) *47 (20)	**.**101
Statins	Yes No	63 (2) 2361 (75) *533 (20)	2 (1) 204 (87) *29 (12)	**.148**

Familial and Genetic Factors				
APOE Genotype	One or Two E2 E3/E3 One E4 Two E4			.794
Family History of AD	Yes No	132 (5) 2021 (75) *533 (20)	23 (10) 207 (88) *5 (2)	**.024**
Family History of Senile Dementia	Yes No	133 (5) 1982 (74) *571 (21)	9 (4) 197 (84) *29 (12)	.272
Family History of Mongolism	Yes No	22 (1) 2076 (77) *588 (22)	4 (2) 181 (77) *50 (21)	**.171**
Family History of Mental Retardation	Yes No	35 (1) 2038 (76) *613 (23)	5 (2) 173 (74) *57 (24)	.277
Other Exposures				
Occupational Exposure to Glues	Yes No	189 (7) 2019 (75) *478 (18)	12 (5) 154 (66) *69 (29)	.552
Occupational Exposure to Solvents	Yes No	159 (6) 2049 (76) *478 (18)	10 (4) 155 (66) *70 (30)	.583
Occupational Exposure to Pesticides	Yes No	169 (6) 2043 (76) *474 (18)	6 (3) 160 (68) *69 (29)	**.055**
Influenza Shot	Yes No	1255 (47) 1015 (38) *416 (15)	104 (44) 87 (37) *44 (19)	.823
Polio Shot	Yes No	618 (23) 1589 (59) *479 (18)	23 (10) 159 (68) *53 (23)	**.000**
Diptheria Shot	Yes No	551 (21) 1623 (60) *512 (19)	22 (9) 162 (69) *51 (22)	**.000**
Tetanus Shot	Yes No	709 (26) 1496 (56) *481 (18)	30 (13) 154 (66) *51 (22)	**.000**

Includes Cases of CLoND in Reduced-Cause CIND group; compared to all normals without CLoND
*missing data

BIVARIATE ANALYSIS: ALL-CAUSE CIND VERSUS COGNITIVELY NORMAL

Variable		Cognitively Normal-2 (n=2698)	CIND-2 (n=390)	p-value
Health Conditions				
Heart Attack-1	Yes No	171 (6) 1893 (70) *634 (23)	32 (8) 347 (89) *11 (2)	.918
Diabetes-1	Yes No	237 (9) 2461 (91) * 0	43 (11) 347 (89) *0	**.150**
Diabetes-2	Yes No	324 (12) 2370 (88) *4 (0)	59 (15) 331 (85) *0 (0)	**.083**
Stroke-1	Yes No	80 (3) 2616 (97) *2 (0)	33 (8) 357 (92) *0	**.000**
Stroke-2	Yes No	162 (6) 2525 (93) *11 (0)	67 (17) 322 (83) *1 (0)	**.000**
High Blood Pressure-1	Yes No	1071 (40) 1627 (60) *0	161 (41) 228 (58) *1 (0)	.524
High Blood Pressure-2	Yes No	1167 (43) 1521 (56) *10 (0)	188 (48) 202 (52) *0	**.075**
Parkinson's disease-1	Yes No	14 (1) 2682 (99) *2(0)	14 (4) 376 (96) *0	**.000**
Parkinson's disease-2	Yes No	49 (2) 2633 (98) 16 (1)	17 (4) 372 (95) 1 (0)	**.001**
Thyroid Condition-1	Yes No	455 (17) 1645 (61) *598 (22)	51 (13) 318 (82) *21 (5)	**.001**
Arthritis-1	Yes No	1691 (63) 999 (37) 8 (0)	245 (63) 132 (34) *13 (3)	.423
Kidney Disease-1	Yes No	289 (11) 2398 (89) *11 (0)	53 (14) 325 (83) *12 (3)	**.059**
Epilepsy-1	Yes No	17 (1) 2021 (75) *660 (24)	6 (2) 375 (96) *9 (2)	**.172**
Self or Proxy Reported Depression	Yes No	259 (10) 1701 (63) *738 (27)	67 (17) 222 (57) *101 (26)	**.000**
Self or Proxy Reported Depression-2	Yes No	243 (9) 2229 (83) 226 (8)	82 (21) 300 (77) 8 (2)	**.000**
Other Psychiatric Illness	Yes No	545 (20) 2150 (80) *3 (0)	137 (35) 251 (64) *2 (1)	**.000**
Demographic Information				
Age-1	65-74 75-84 85 & over	1493 (55) 1049 (39) 156 (6)	114 (29) 189 (48) 87 (22)	**.000**
Age-2	65-74 75-84 85 & over	857 (32) 1406 (52) 435 (16)	45 (12) 172 (44) 173 (44)	**.000**

Marital Status-1	Currently/ Common Law Separated/ Divorced Widowed Never	1125 (42) 116 (4) 1212 (45) 243 (9) *2 (0)	91 (23) 23 (6) 238 (61) 37 (9) *1 (0)	**.000**
Marital Status-2	Currently/ Common Law Divorced/ Separated Widowed Never	856 (32) 101 (4) 1492 (55) 244 (9) *5(0)	62 (16) 18 (5) 273 (70) 37 (9) *0 (0)	**.000**
Education	6 yrs & less 7-9 yrs 10-12 yrs 13 + yrs	248 (9) 703 (26) 1020 (38) 718(27) *9 (0)	103 (26) 113 (29) 120 (31) 53 (14) *1 (0)	**.000**
Income	<$19,999 $20,000- 34,999 $35,000- 49,999 $50,000 +	1167 (43) 648 (24) 272 (10) 189 (7) *422 (16)	229 (59) 43 (11) 13 (3) 7 (2) *98 (25)	**.000**
Rural/ Urban	Rural Urban	275 (10) 2419 (90) *4 (0)	45 (12) 344 (88) *1 (0)	.411
Region-1	Atlantic Quebec Ontario Prairies B.C.	490 (18) 535 (20) 529 (20) 606 (22) 538 (20)	72 (18) 116 (30) 74 (19) 66 (17) 62 (16)	**.000**
Region-2	Atlantic Quebec Ontario Prairies B.C.	488 (18) 533 (20) 533 (20) 603 (22) 541 (20)	72 (18) 115 (29) 75 (19) 66 (17) 62 (16)	**.000**
Residential Status-1	Institution Community	38 (1) 2660 (99) *0	40 (10) 350 (90) *0	**.000**
Residential Status-2	Institution Community	106 (4) 2592 (96) *0	85 (22) 305 (78) *0	**.000**

Lifestyle Factors				
Smoking Status	Yes No	908 (34) 1500 (56) *290 (11%)	104 (27) 281 (72) *5 (1)	**.000**
Regular Spirit Drinking	Yes No	428 (16) 1924 (71) *346 (13)	45 (12) 275 (71) *70 (18)	**.069**
Regular Wine Drinking	Yes No	356 (13) 1991 (74) *351 (13)	32 (8) 290 (74) *68 (17)	**.013**

Regular Coffee Drinking		Yes No	1711 (63) 679 (25) *308 (11)	210 (54) 116 (30) *64 (16)	**.008**
Regular Tea Drinking		Yes No	1726 (64) 660 (24) *312 (12)	239 (61) 80 (21) *71 (18)	.331
Regular Shellfish Consumption		Yes No	525 (19) 1831 (68) *342 (13)	41 (11) 273 (70) *76 (19)	**.000**
Vitamin E		Yes No	198(7) 2235(83) *65 (10)	10(3) 321(82) *59 (15)	**.001**
Vitamin C		Yes No	180(7) 2253(84) *265 (10)	13(3) 318 (82) *59 (15)	**.020**
Vitamin B		Yes No	99 (4) 2334 (87) *265 (10)	10 (3) 321 (82) *59 (15)	.358
Multi-vitamin		Yes No	457(17) 1976 (73) *265 (10)	37 (9) 294 (75) *59 (15)	**.001**
Regular Exercise		Yes No No	1607 (60) 758 (28) *333 (12)	164 (42) 158 (41) *68 (17)	**.000**
Head Injury		Yes No	328 (12) 1967 (73) *403 (15)	61 (16) 327 (84) *2 (1)	.459
Medication Usage					
HRT Use	Ever Never		791 (29) 1907 (71) *0	72 (18) 318 (82) *0	**.000**
HRT Duration	<12 mths 13 mths – 5 yrs 61 mths – 10 yrs >121 mths		196 (25) 205 (26) 91 (12) 208 (26) *91 (12)	21 (29) 14 (19) 5 (7) 9 (13) *23 (32)	**.121**
Age at First HRT Use	40 yrs & under 41-50 yrs 51 – 60 yrs 60 yrs & over		109 (14) 352 (45) 189 (24) 90 (11) *51 (6)	12 (17) 26 (36) 16 (22) 8 (11) *10 (14)	.747
Regular use of Painkillers	Yes No		1231 (60) 1122 (42) *345 (13)	153 (39) 148 (38) *89 (23)	**.**627
Statins	Yes No		63(2) 2370(88) *265 (10)	3(1) 328(84) *59 (15)	**.060**
Familial and Genetic Factors					
APOE Genotype		One or Two E2 E3/E3 One E4 Two E4	40 229 71 1	31 146 48 1	.751
Family History of AD		Yes No	132 (5) 2029 (75) *537 (20)	36 (9) 341 (87) *13 (3)	**.013**

Family History of Senile Dementia	Yes No	130 (5) 1982 (73) *586 (22)	17 (4) 320 (82) *53 (14)	.425
Family History of Mongolism	Yes No	22 (1) 2070 (77) *606 (22)	5 (1) 289 (74) 96 (25)	.325
Family History of Mental Retardation	Yes No	35 (1) 2046 (76) *617 (23)	9 (2) 283 (73) *98 (25)	**.097**
Other Exposures				
Occupational Exposure to Glues	Yes No	189(7) 2028(75) *481 (18)	20 (5) 251(64) *119 (31)	.521
Occupational Exposure to Solvents	Yes No	159 (6) 2058 (76) *481 (18)	24 (6) 246 (63) *120 (31)	.308
Occupational Exposure to Pesticides	Yes No	169 (6) 2052 (76) *477 (18)	16 (4) 252 (65) *122 (31)	.334
Influenza Shot	Yes No	1259 (47) 1020 (38) *419 (16)	164 (42) 148 (38) *78 (20)	.372
Polio Shot	Yes No	621 (23) 1595 (59) *482 (18)	42 (11) 252 (65) *96 (25)	**.000**
Diptheria Shot	Yes No	553 (20) 1629 (60) *516 (19)	35 (9) 264 (68) *91 (23)	**.000**
Tetanus Shot	Yes	710 (26) 1503 (56) *485 (18)	45 (12) 255 (65) *90 (23)	**.000**

*missing data

BIVARIATE ANALYSIS: REDUCED-CAUSE CIND VERSUS COGNITIVELY NORMAL

Variable		Cognitively Normal-2 (n=2698)	CIND (n=297)	P-value
Health Conditions				
Heart Attack-1	Yes No	171 (6) 1893 (70) *634 (23)	26 (9) 266 (90) *5 (2)	.721
Diabetes-1	Yes No	237 (9) 2461 (91) * 0	30 (10) 267 (90) *0	.450
Diabetes-2	Yes No	324 (12) 2370 (88) *4 (0)	41 (13) 256 (86) *1 (0)	**.**374
Stroke-1	Yes No	80 (3) 2616 (97) *2 (0)	28 (9) 269 (91) *0	**.000**
Stroke-2	Yes No	162 (6) 2525 (93) *11 (0)	60 (20) 236 (81) *1 (0)	**.000**
High Blood Pressure-1	Yes No	1071 (40) 1627 (60) *0	126 (42) 170 (57) *1 (0)	.338
High Blood Pressure-2	Yes No	1167 (43) 1521 (56) *10 (0)	148 (50) 149 (50) *0	**.035**
Parkinson's disease-1	Yes No	14 (1) 2682 (99) *2(0)	11 (4) 286 (96) *0	**.000**
Parkinson's disease-2	Yes No	49 (2) 2633 (98) *16 (1)	14 (5) 283 (95) *0 (0)	**.001**
Thyroid Condition-1	Yes No	455 (17) 1645 (61) *598 (22)	39 (13) 246 (83) *12 (4)	**.002**
Arthritis-1	Yes No	1691 (63) 999 (37) 8 (0)	193 (65) 95 (32) *9 (3)	**.165**
Kidney Disease-1	Yes No	289 (11) 2398 (89) *11 (0)	45 (15) 244 (82) *8 (3)	**.014**
Epilepsy-1	Yes No	17 (1) 2021 (75) *660 (24)	5 (2) 292 (98) *0 (0)	**.157**
Self or Proxy Reported Depression-1	Yes No	259 (10) 1701 (63) *738 (27)	43 (15) 175 (58) *79 (27)	**.008**
Self or Proxy Reported Depression-2	Yes No	243 (9) 2229 (83) *226 (8)	63 (21) 234 (79) 0	**.000**
Other Psychiatric Illness	Yes No	545 (20) 2150 (80) *3 (0)	91 (31) 204 (69) *2 (1)	**.000**
Demographic Information				
Age-1	65-74 75-84 85 & over	1493 (55) 1049 (39) 156 (6)	77 (26) 154 (52) 66 (22)	**.000**

Age-2	65-74 75-84 85 & over	857 (32) 1406 (52) 435 (16)	28 (9) 134 (45) 135 (46)	**.000**
Marital Status-1	Currently/ Common Law Separated/ Divorced Widowed Never	1125 (42) 116 (4) 1212 (45) 243 (9) *2 (0)	69 (23) 17 (6) 184 (62) 26 (9) *1 (0)	**.000**
Marital Status-2	Currently/ Common Law Separated/ Divorced Widowed Never	856 (32) 101 (4) 1492 (55) 244 (9) *5 (0)	46 (2) 14 (1) 211 (8) 26 (1) *0 (0)	**.000**
Education	6 yrs & under 7-9 yrs 10-12 yrs 13 + yrs	248 (9) 703 (26) 1020 (38) 718(27) *9 (0)	77 (26) 78 (26) 96 (32) 45 (15) *1 (0)	**.000**
Income	<$19,999 $20,000- 34,999 $35,000- 49,999 $50,000 +	1167 (43) 648 (24) 272 (10) 189 (7) *422 (16)	170 (57) 38 (13) 12 (4) 5 (2) *72(24)	**.000**
Rural/ Urban	Rural Urban	275 (10) 2419 (90) *4 (0)	30 (10) 266 (90) *1 (0)	.969
Region-1	Atlantic Quebec Ontario Prairies B.C.	490 (18) 535 (20) 529 (20) 606 (22) 538 (20)	41 (14) 99 (33) 65 (22) 49 (17) 43 (15)	**.000**
Region-2	Atlantic Quebec Ontario Prairies B.C.	488 (18) 533 (20) 533 (20) 603 (22) 541 (20)	41 (14) 98 (33) 66 (22) 49 (17) 43 (16)	**.000**
Residential Status-1	Institution Community	38 (1) 2660 (99) *0	27 (9) 270 (91) *0	**.000**
Residential Status-2	Institution Community	106 (4) 2592 (96) *0	59 (20) 238 (80) *0	**.000**
Lifestyle Factors				
Smoking Status	Yes No	908 (34) 1500 (56) *290 (11%)	76 (26) 216 (73) *5 (2)	**.000**

Regular Spirit Drinking	Yes No	428 (16) 1924 (71) *346 (13)	33 (11) 214 (72) *50 (17)	**.058**
Regular Wine Drinking	Yes No	356 (13) 1991 (74) *351 (13)	24 (8) 224 (75) *49 (16)	**.020**
Regular Coffee Drinking	Yes No	1711 (63) 679 (25) *308 (11)	172 (58) 80 (27) *45 (15)	.266
Regular Tea Drinking	Yes No	1726 (34) 660 (24) *312 (12)	176 (59) 67 (23) *54 (18)	.976
Regular Shellfish Consumption	Yes No	525 (19) 1831 (68) *342 (13)	41 (11) 273 (70) *76 (19)	**.000**
Vitamin E	Yes No	198(7) 2235(83) *65 (10)	10 (3) 244 (82) *43 (14)	**.017**
Vitamin C	Yes No	180(7) 2253(84) *265 (10)	12 (4) 242 (81) *43 (14)	**.115**
Vitamin B	Yes No	99 (4) 2334 (87) *265 (10)	8 (3) 246 (83) *43 (14)	.476
Multi-vitamin	Yes No	457(17) 1976 (73) *265 (10)	33 (11) 221 (74) *43 (14)	**.023**
Regular Exercise	Yes No	1607 (60) 758 (28) *333 (12)	123 (41) 123 (41) *51 (17)	**.000**
Head Injury	Yes No	328 (12) 1967 (73) *403 (15)	46 (15) 251 (85) *0	.581
Medication Usage				
HRT Use	Ever Never	791 (29) 1907 (71) *0	63 (21) 234 (79) *0	**.003**
HRT Duration	<12 mths 13 mths – 5 yrs 61 mths – 10 yrs >121 mths	196 (25) 205 (26) 91 (12) 208 (26) *91 (12)	20 (32) 11 (17) 5 (8) 9 (14) *18 (29)	**.086**
Age at First HRT Use	40 yrs & under 41-50 yrs 51 – 60 yrs 60 yrs & over	109 (14) 352 (45) 189 (24) 90 (11) *51 (6)	11 (17) 21 (33) 15 (24) 7 (11) *9 (14)	.574
Regular use of Painkillers	Yes No	1231 (60) 1122 (42) *345 (13)	117 (39) 117 (39) *63 (21)	**.**499
Statins	Yes No	63(2) 2370(88) *265 (10)	2 (1) 252 (85) *43 (14)	**.085**

Familial and Genetic Factors				
APOE Genotype	One or Two E2 E3/E3 One E4 Two E4	40 229 71 1	26 116 37 1	.794
Family History of AD	Yes No	132 (5) 2029 (75) *537 (20)	25 (8) 264 (89) *8 (3)	**.097**
Family History of Senile Dementia	Yes No	130 (5) 1982 (73) *586 (22)	11 (4) 246 (83) *40 (13)	**.230**
Family History of Mongolism	Yes No	22 (1) 2070 (77) *606 (22)	5 (2) 218 (73) 74 (25)	**.115**
Family History of Mental Retardation	Yes No	35 (1) 2046 (76) *617 (23)	5 (2) 216 (73) *76 (26)	.530
Other Exposures				
Occupational Exposure to Glues	Yes No	189(7) 2028(75) *481 (18)	15 (5) 191 (64) *91 (31)	.539
Occupational Exposure to Solvents	Yes No	159 (6) 2058 (76) *481 (18)	13 (4) 192 (65) *92 (31)	.658
Occupational Exposure to Pesticides	Yes No	169 (6) 2052 (76) *477 (18)	9 (3) 197 (66) *91 (31)	**.088**
Influenza Shot	Yes No	1259 (47) 1020 (38) *419 (16)	132 (44) 105 (35) *60 (20)	.894
Polio Shot	Yes No	621 (23) 1595 (59) *482 (18)	33 (11) 189 (64) *75 (25)	**.000**
Diptheria Shot	Yes No	553 (20) 1629 (60) *516 (19)	29 (10) 197 (66) *71 (24)	**.000**
Tetanus Shot	Yes	710 (26) 1503 (56) *485 (18)	37 (12) 190 (64) *70 (24)	**.000**

*missing data

BIVARIATE ANALYSIS: ALZHEIMER'S DISEASE VS. COGNITIVELY NORMAL (P<.25)

Variable Name	P-value	Exp (B)	95% CI Exp (B)
Demographic Information			
Age-1			
65-74 (ref)	.000		
75-84	.000	7.299	4.278 – 12.452
85& older	.000	29.143	16.780 – 50.614
Age-2			
65-74 (ref)	.000		
75-84	.001	3.337	1.641 – 6.786
85& older	.000	19.621	9.923 – 38.797
Education			
0 – 6 years	.000	2.765	1.674 – 4.568
7 – 9 years	.024	1.670	1.069 – 2.610
10 – 12 years	.795	1.062	0.675 – 1.672
13 + years (ref)	.000		
Income-2			
< 19,999	.040	2.571	1.042-6.343
20,000 – 34,999	.847	1.102	0.412-2.952
35,000 – 49,999	.572	0.700	0.203-2.417
50,000 + (ref)	.000		
Marital Status-1			
Currently (ref)	.000		
Separated/ Divorced	.178	.256	.035-1.861
Widowed	.000	1.649	1.833-3.827
Never Married	.584	1.215	.605-2.439
Marital Status-2			
Currently (ref)	.000		
Separated/ Divorced	.561	.653	.155-2.750
Widowed	.000	2.598	1.701-3.969
Never Married	.286	1.468	.725-2.972
Institutional Status-1	.000	7.403	4.578 -11.970
Institutional Status-2	.000	14.033	10.264-19.186
Rural-Urban (urban)	.198	0.668	0.362-1.234
Region-1			
B.C. (ref)	.017		
Atlantic	.001	2.795	1.549-5.045
Quebec	.005	2.359	1.288-4.320
Ontario	.026	2.012	1.086-3.727
Prairies	.013	2.140	1.177-3.892
Region-2			
B.C. (ref)	.011		
Atlantic	.000	2.886	1.602 – 5.199
Quebec	.005	2.382	1.301 – 4.361
Ontario	.027	2.009	1.084 – 3.721
Prairies	.015	2.109	1.158 – 3.844
Health Conditions and Illness			
Arthritis-1 (Yes)	.554	1.101	0.800 – 1.517
Thyroid condition-1 (Yes)	.172	1.342	0.880 – 2.046
Heart Attack-1 (No)	.609	1.149	0.675 – 1.956
Kidney Condition or Disease-1 (No)	.812	0.939	0.560 – 1.575
Epilepsy-1 (No)	.153	0.361	0.089 – 1.462
Diabetes-1 (No)	.999	1.00	0.567 – 1.764
Diabetes-2 (No)	.348	0.775	0.456 – 1.319
Stroke-1 (No)	.040	1.778	1.028 – 3.077
Stroke-2 (No)	.004	2.040	1.249 – 3.331
High BP-1 (No)	.199	0.808	0.585 – 1.118
High BP-2 (No)	.090	1.306	0.959 – 1.779
Parkinson's Disease-1 (No)	.887	1.154	0.162 – 8.239

Parkinson's Disease-2 (No)	.105	1.963	0.868 – 4.436
Depression-1 (No)	.001	2.008	1.323 – 3.048
Psychiatric Illness-1 (No)	.959	0.990	0.668 – 1.465
Medication Usage			
HRT (yes)	.001	2.014	1.332 - 3.046
HRT Duration			
12 months or less	.718	1.223	0.411 – 3.639
13 – 60 months	.548	0.679	0.192 – 2.406
61 - 120 months	.374	1.105	0.046 – 3.182
121- 660 months (ref)	.629		
Age at 1st HRT Use			
40 yrs & under (ref)	.537		
41 – 50 years	.648	0.730	0.189 – 2.822
51 – 60 years	.533	1.525	0.405 – 5.750
61 years & older	.825	0.817	0.137 – 4.889
Painkiller Use-1 (Yes)	.957	0.990	0.668 - 1.424
Statins (Yes)	.476	1.661	0.411 – 6.713
Lifestyle Factors			
Coffee-1 (Yes)	.000	1.982	1.401 – 2.804
Tea-1 (Yes)	.024	0.594	0.378 – 0.933
Wine-1 (Yes)	.004	3.389	1.492 – 7.698
Spirit-1 (Yes)	.035	1.856	1.045 – 3.297
Smoker-1 (Yes)	.000	2.016	1.390 – 2.922
Exercise-1 (Yes)	.000	2.233	1.577 – 3.163
Vitamin E (yes)	.043	2.790	1.031 – 7.548
Vitamin C (yes)	.135	1.975	0.808 – 4.827
Multi-vitamin (yes)	.157	1.431	0.871 - 2.353
Vitamin B (yes)	.563	1.342	0.496 – 3.630
Shellfish-1 (yes)	.163	1.397	0.873 – 2.233
Head Injury-1 (No)	.520	0.854	0.529 – 1.380
Familial and Genetic Factors			
APOE			
One or Two E2 Alleles (ref)	.000		
E3/E3 Alleles	.449	0.784	0.417 – 1.472
One E4 Allele	.370	1.360	0.694 – 2.666
Two E4 Alleles	.000	7.607	2.448 – 23.638
Family History of AD (no)	.018	0.545	0.330 – 0.903
Family History of Senility (no)	.196	0.555	0.227 – 1.354
Family History of Mongolism (no)	.552	1.528	0.378 – 6.183
Family History of Mental Retardation (no)	.979	1.019	0.252 – 4.125
Other Exposures			
Influenza Shot (yes)	.772	0.949	0.668 – 1.350
Polio Shot (yes)	.000	4.387	2.299 – 8.369
Diptheria Shot (yes)	.000	3.461	1.865 – 6.426
Tetanus Shot (yes)	.000	4.794	2.583 – 8.898
Exposure to Solvents (no)	.136	0.468	0.173 – 1.270
Exposure to Pesticides (no)	.790	0.907	0.442 – 1.860
Exposure to Glues (no)	.357	0.698	0.325 – 1.500

BIVARIATE ANALYSIS: VASCULAR DEMENTIA VS. COGNITIVELY NORMAL (P<.25)

Variable Name	P-value	Exp (B)	95% CI Exp (B)
Demographic Information			
Age-1			
65-74 (ref)	.000		
75-84	.000	6.585	2.726 – 15.902
85& older	.000	10.787	3.624 – 32.110
Age-2			
65-74 (ref)	.000		
75-84	.013	12.693	1.707 – 94.361
85& older	.000	36.451	4.879 – 272.314
Education			
0 – 6 years	.000	6.691	2.571 – 17.412
7 – 9 years	.420	1.530	0.545 – 4.299
10 – 12 years	.622	1.285	0.475 – 3.474
13 + years (ref)	.000		
Income-2			
< 19,999	.160	4.181	0.567-30.810
20,000 – 34,999	.660	.583	0.053-6.429
35,000 – 49,999	.526	2.081	0.216-20.005
50,000 + (ref)	.023		
Marital Status-1			
Currently (ref)	.348		
Separated/Divorced	.970	.000	.000-E
Widowed	.082	1.850	.925-3.699
Never Married	.217	1.930	.680-5.479
Marital Status-2			
Currently (ref)	.131		
Separated/Divorced	.974	.000	NA
Widowed	.019	2.844	1.184-6.834
Never Married	.077	2.914	.889-9.548
Institutional Status-1 (community)	.000	8.959	3.51-22.868
Institutional Status-2 (community)	.000	19.326	10.45-35.73
Rural-Urban (ref urban)	.017	2.463	1.18-5.16
Region-1			
B.C. (ref)	.403		
Atlantic	.732	1.231	.375-4.043
Quebec	.279	1.828	.613-5.456
Ontario	.584	1.378	.437-4.344
Prairies	.094	2.394	.862-6.650
Region-2			
B.C. (ref)	.391		
Atlantic	.720	1.243	0.375 – 4.083
Quebec	.272	1.846	0.619 – 5.508
Ontario	.587	1.375	0.436 – 4.335
Prairies	.090	2.420	0.871 – 6.722
Health Conditions and Illness			
Arthritis-1 (Yes)	.631	0.849	0.437 – 1.653
Thyroid condition-1 (Yes)	.891	1.053	0.501 – 2.213
Heart Attack-1 (No)	.008	2.884	1.322 – 6.290
Kidney Condition or Disease-1 (No)	.067	2.065	0.952 – 4.481
Epilepsy-1 (No)	.041	8.153	1.085 – 61.264

Diabetes-1 (No)	.645	1.275	0.453 – 3.587
Diabetes-2 (No)	.299	1.539	0.682 – 3.472
Stroke-1 (No)	.000	4.614	2.131 – 9.990
Stroke-2 (No)	.000	53.591	25.574 – 112.300
High BP-1 (No)	.003	2.595	1.375 – 4.900
High BP-2 (No)	.000	3.509	1.759 – 7.002
Parkinson's Disease-1 (No)	.755	0.049	NA
Parkinson's Disease-2	.168	2.719	06.57-11.261
Depression-1 (No)	.022	2.834	1.166 – 6.888
Psychiatric Illness-1 (No)	.080	1.836	0.930 – 3.624
Medication Usage			
HRT (yes)	.006	5.200	1.605 – 16.845
HRT Duration (all types)			NA
Age at 1st HRT Use			NA
Painkiller Use-1 (Yes)	.224	0.619	0.286 – 1.342
Statins	.569	20.886	NA
Lifestyle Factors			
Coffee-1 (Yes)	.982	0.991	0.436 – 2.250
Tea-1 (Yes)	.781	0.886	0.376 – 2.085
Wine-1 (Yes)	.574	1.411	0.425 – 4.687
Spirit-1 (Yes)	.087	5.707	0.774 – 42.061
Smoker-1 (Yes)	.159	0.609	0.305 – 1.215
Exercise-1 (Yes)	.020	2.415	1.149 – 5.075
Vitamin E (yes)	.305	22.844	NA
Vitamin C (yes)	.456	2.137	0.290 – 15.729
Multi-vitamin (yes)	.291	1.907	0.576 – 6.318
Vitamin B (yes)	.901	1.136	0.154 – 8.357
Shellfish-1	.045	7.711	1.048 – 56.744
Head Injury-1 (no)	.118	1.807	0.860 – 3.795
Familial and Genetic Factors			
APOE			
One or Two E2 Alleles (ref)	.076		
E3/E3 Alleles	.441	2.223	0.291 – 16.994
One E4 Allele	.094	5.758	0.743 – 44.599
Two E4 Alleles	.982	0.000	NA
Family History of AD (no)	.283	1.763	0.627 – 4.962
Family History of Senility (no)	.561	1.421	0.435 –4.641
Family History of Mongolism (no)	.741	0.049	NA
Family History of Mental Retardation (no)	.680	0.049	NA
Other Exposures			
Influenza Shot (yes)	.414	0.722	0.331 – 1.577
Polio Shot (yes)	.089	2.844	0.851 – 9.503
Diptheria Shot (yes)	.066	3.882	0.915 – 16.467
Tetanus Shot (yes)	.147	2.221	0.755 – 6.529
Exposure to Solvents (no)	.289	1.928	0.573 – 6.489
Exposure to Pesticides (no)	.338	1.811	0.538 – 6.093
Exposure to Glues (no)	.449	1.599	0.475 – 5.381

NA- not enough cases to get a stable estimate

APPENDIX D

Hand Calculations for Interaction Assessment

Interaction Assessment : CLoND

Interaction Term : HRT * Family History of AD

$$l(h,e,z) = \beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1 + \beta_z$$

	e_0	e_1	
h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_2$
$= 1.215$
$\exp(B) = OR = 3.371$

$v(\hat{d}_1) = v(\beta_2)$
$= (.348)^2 = .12$
95% CI = 1.703 - 6.671

$\hat{d}_2 = \beta_2 + \beta_3$
$= 1.612 + (-1.353)$
$= 0.259$
$\exp(B) = OR = 1.30$

$v(\hat{d}_2) = v(\beta_2) + v(\beta_3) + 2\,cov(\beta_2, \beta_3)$
$= (.535)^2 + (.666)^2 + 2[-.806 (.535)(.666)]$
$= 0.16$
95% CI = 0.59 - 2.84

$\hat{d}_3 = \beta_1$
$= .138$
$\exp(B) = OR = 1.148$

$v(\hat{d}_3) = v(\beta_1)$
$= (.240)^2 = 0.06$
95% CI = 0.717 - 1.839

$\hat{d}_4 = \beta_1 + \beta_3$
$= .138 + (-1.353)$
$= -1.215$
$\exp(B) = OR = 0.30$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_3) + 2\,cov(\beta_1, \beta_3)$
$= (.240)^2 + (.666)^2 + 2[-.337 (.240)(.666)]$
$= .39$
95% CI = 0.09 - 1.01

Interaction Assessment: All-Cause CIND

Interaction Term: HRT * Education

$$l(h_1, e_{1,2}) = \beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 e_2 + \beta_4 e_3 + \beta_5 h_1 e_1 + \beta_6 h_1 e_2 + \beta_7 h_1 e_3 + \beta_2'$$

	e_0	e_1	
h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_5 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

For e_1 (6 years or less):

$\hat{d}_1 = \beta_2$
$= 1.255$
$Exp(B) = OR = 3.508$

$v(\hat{d}_1) = v(\beta_2)$
$= (.536)^2 = 0.29$
95% CI = 1.226 - 10.035

$\hat{d}_2 = \beta_2 + \beta_5$
$= 1.255 + .625$
$= 1.880$
$Exp(B) = OR = 6.55$

$v(\hat{d}_2) = v(\beta_2) + v(\beta_5) + 2cov(\beta_2, \beta_5)$
$= (.536)^2 + (.619)^2 + 2[-.855 (.536)(.619)]$
$= 0.10$
95% CI = 3.49 - 12.29

$\hat{d}_3 = \beta_1$
$= .265$
$Exp(B) = OR = 1.30$

$v(\hat{d}_3) = v(\beta_1)$
$= (.483)^2 = .23$
95% CI = 0.506 - 3.360

$\hat{d}_4 = \beta_1 + \beta_5$
$= 0.265 + .625$
$= 0.890$
$p(B) = OR = 2.44$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_5) + 2cov(\beta_1, \beta_5)$
$= (.483)^2 + (.619)^2 + 2[-.640 (.483)(.619)]$
$= 0.23$
95% CI = 0.95 - 6.23

For e_2 (7-9 years):

	e_0	e_2	
h_0	β_0	$\beta_0+\beta_3 e_2$	$\hat{d}_1$
h_1	$\beta_0+\beta_1 h_1$	$\beta_0+\beta_1 h_1+\beta_3 e_2+\beta_6 h_1 e_2$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_3$
$= .991$
$Exp(B) = OR = 2.69$

$v(\hat{d}_1) = v(\beta_3)$
$= (.466)^2 = .22$
$95\%\ CI = 1.081 - 6.713$

$\hat{d}_2 = \beta_3 + \beta_6$
$= .991 + (-.361)$
$= .630$
$Exp(B) = OR = 1.88$

$v(\hat{d}_2) = v(\beta_3) + v(\beta_6) + 2cov(\beta_3, \beta_6)$
$= (.466)^2 + (.552)^2 + 2[-.841 (.466)(.552)]$
$= 0.09$
$95\%\ CI = 1.34 - 3.78$

$\hat{d}_3 = \beta_1$
$= .265$
$Exp(B) = OR = 1.30$

$v(\hat{d}_3) = v(\beta_1)$
$= (.483)^2 = .23$
$95\%\ CI = 0.506 - 3.360$

$\hat{d}_4 = \beta_1 + \beta_6$
$= .265 + (-.361)$
$= -.096$
$Exp(B) = OR = 0.91$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_6) + 2cov(\beta_1, \beta_6)$
$= (.483)^2 + (.552)^2 + 2[-.841 (.483)(.552)]$
$= 0.08$
$95\%\ CI = 0.52 - 1.58$

For e_3 (10-12 years):

	e_0	e_3	
h_0	β_0	$\beta_0 + \beta_4 e_3$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_4 e_3 + \beta_7 h_1 e_3$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_4$
$= -.496$
$\text{Exp}(B) - OR = 0.61$

$v(\hat{d}_1) = v(\beta_4)$
$= (.503)^2 = 0.25$
95% CI = 0.227 - 1.634

$\hat{d}_2 = \beta_4 + \beta_7$
$= -.496 + 1.149$
$= 0.653$
$\text{Exp}(B) = OR = 1.92$

$v(\hat{d}_2) = v(\beta_4) + v(\beta_7) + 2\,\text{cov}(\beta_4, \beta_7)$
$= (.503)^2 + (.577)^2 + 2[-.873 (.503)(.577)]$
$= 0.07$
95% CI = 1.14 - 3.23

$\hat{d}_3 = \beta_1$
$= .265$
$\text{Exp}(B) = OR = 1.30$

$v(\hat{d}_3) = v(\beta_1)$
$= (.483)^2 = 0.23$
95% CI = 0.506 - 3.360

$\hat{d}_4 = \beta_1 + \beta_7$
$= .265 + 1.149$
$= 1.414$
$\text{Exp}(B) = OR = 4.11$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_7) + 2\,\text{cov}(\beta_1, \beta_7)$
$= (.503)^2 + (.577)^2 + 2[-.646 (.503)(.577)]$
$= .21$
95% CI = 1.68 - 10.10

Interaction Term: HRT * Exercise

$l(h, e, z) = \beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$

	e_0	e_1	
h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_2$
$= 1.049$
$\text{Exp}(B) = OR = 2.85$

$v(\hat{d}_1) = v(\beta_2)$
$= (.341)^2 = .12$
95% CI = 1.464 - 5.563

$\hat{d}_2 = \beta_2 + \beta_3$
$= 1.049 + (-.823)$
$= 0.226$
$\text{Exp}(B) = OR = 1.25$

$v(\hat{d}_2) = v(\beta_2) + v(\beta_3) + 2\,\text{cov}(\beta_2, \beta_3)$
$= (.341)^2 + (.391)^2 + 2[-.870 (.341)(.391)]$
$= 0.04$
95% CI = 0.85 - 1.86

$\hat{d}_3 = \beta_1$
$= .265$
$\text{Exp}(B) = OR = 1.30$

$v(\hat{d}_3) = v(\beta_1)$
$= (.483)^2 = 0.23$
95% CI = 0.506 - 3.360

$\hat{d}_4 = \beta_1 + \beta_3$
$= .265 + (-.823)$
$= -0.558$
$\text{Exp}(B) = OR = 0.57$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_3) + 2\,\text{cov}(\beta_1, \beta_3)$
$= (.483)^2 + (.391)^2 + 2[.009 (.483)(.391)]$
$= .38$
95% CI = 0.17 - 1.93

Interaction Term: HRT * Family History of AD

$l(h, e, z) = \beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$

	e_0	e_1	
h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_2$
$= 1.914$
$\text{Exp}(B) = OR = 6.78$

$r(\hat{d}_1) = r(\beta_2)$
$= (.503)^2$
$= .25$
95% CI = 2.529 - 18.18

$\hat{d}_2 = \beta_2 + \beta_3$
$= 1.914 + (-1.325)$
$= 0.589$
$\text{Exp}(B) = OR = 1.80$

$r(\hat{d}_2) = r(\beta_2) + r(\beta_3) + 2\,\text{cov}(\beta_2, \beta_3)$
$= (.503)^2 + (.594)^2 + 2[-.849 (.503)(.594)]$
$= .09$
95% CI = 1.00 - 3.24

$\hat{d}_3 = \beta_1$
$= .265$
$\text{Exp}(B) = OR = 1.304$

$r(\hat{d}_3) = r(\beta_1)$
$= (.483)^2 = .23$
95% CI = .506 - 3.360

$\hat{d}_4 = \beta_1 + \beta_3$
$= .265 + (-1.325)$
$= 1.06$
$\text{Exp}(B) = OR = 0.35$

$r(\hat{d}_4) = r(\beta_1) + r(\beta_3) + 2\,\text{cov}(\beta_1, \beta_3)$
$= (.483)^2 + (.594)^2 + 2[-.205 (.483)(.594)]$
$= 0.46$
95% CI = 0.09 - 1.31

For e_2 (7–9 years):

	e_0	e_2	
h_0	β_0	$\beta_0 + \beta_3 e_2$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_3 e_2 + \beta_6 h_1 e_2$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_3$
$= .946$
$\text{Exp}(B) = OR = 2.576$

$v(\hat{d}_1) = v(\beta_3)$
$= (.438)^2 = 0.19$
95% CI = 1.091 – 6.084

$\hat{d}_2 = \beta_3 + \beta_6$
$= .946 + (-.410)$
$= .536$
$\text{Exp}(B) = OR = 1.71$

$v(\hat{d}_2) = v(\beta_3) + v(\beta_6) + 2\,\text{cov}(\beta_3, \beta_6)$
$= (.438)^2 + (.534)^2 + 2[-.920(.438)(.534)]$
$= 0.10$
95% CI = 0.92 – 3.18

$\hat{d}_3 = \beta_1$
$= -.196$
$\text{Exp}(B) = OR = .822$

$v(\hat{d}_3) = v(\beta_1)$
$= (.424)^2 = 0.18$
95% CI = .358 – 1.887

$\hat{d}_4 = \beta_1 + \beta_6$
$= -.196 + (-.410)$
$= -.606$
$\text{Exp}(B) = OR = 0.55$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_6) + 2\,\text{cov}(\beta_1, \beta_6)$
$= (.424)^2 + (.534)^2 + 2[-.768(.424)(.534)]$
$= 0.12$
95% CI = 0.28 – 1.08

For e_3 (10-12 years):

	e_0	e_3	
h_0	β_0	$\beta_0 + \beta_4 e_3$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_4 e_3 + \beta_7 h_1 e_3$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_4$
$= -.625$
$\text{Exp}(B) = OR = .535$

$v(\hat{d}_1) = v(\beta_4)$
$= (.492)^2 = 0.24$
95% CI = .204 - 1.405

$\hat{d}_2 = \beta_4 + \beta_7$
$= -.625 + 1.250$
$= 0.625$
$\text{Exp}(B) = OR = 1.87$

$v(\hat{d}_2) = v(\beta_4) + v(\beta_7) + 2\text{cov}(\beta_4, \beta_7)$
$= (.492)^2 + (.568)^2 + 2[-.867 (.492)(.568)]$
$= 0.08$
95% CI = 1.07 - 3.25

$\hat{d}_3 = \beta_1$
$= -.196$
$\text{Exp}(B) = OR = .822$

$v(\hat{d}_3) = v(\beta_1)$
$= (.424)^2 = 0.18$
95% CI = 0.358 - 1.887

$\hat{d}_4 = \beta_1 + \beta_7$
$= -.196 + 1.250$
$= 1.054$
$\text{Exp}(B) = OR = 2.87$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_7) + 2\text{cov}(\beta_1, \beta_7)$
$= (.424)^2 + (.568)^2 + 2[-.696 (.424)(.568)]$
$= 0.16$
95% CI = 1.31 - 6.28

Interaction: HRT * Family History of AD

$l(h_1, e_{1,2}) = \beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$

(h_0: c_0; e_1)

h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_3 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_2$
$= 1.780$
$\text{Exp}(B) - OR = 5.929$

$v(\hat{d}_1) = v(\beta_2)$
$= (.467)^2 = .22$
95% CI = 2.376 - 14.799

$\hat{d}_2 = \beta_2 + \beta_3$
$= 1.780 + (-1.581)$
$= 0.199$
$\text{Exp}(B) = OR = 1.22$

$v(\hat{d}_2) = v(\beta_2) + v(\beta_3) + 2\text{cov}(\beta_2, \beta_3)$
$= (.467)^2 + (.590)^2 + 2[-.790 (.467)(.570)]$
$= 0.11$
95% CI = 0.64 - 2.34

$\hat{d}_3 = \beta_1$
$= -.196$
$\text{Exp}(B) - OR = 0.822$

$v(\hat{d}_3) = v(\beta_1)$
$= (.424)^2 = .18$
95% CI = 0.358 - 1.887

$\hat{d}_4 = \beta_1 + \beta_3$
$= -0.196 + (-1.581)$
$= -1.777$
$= 0.17$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_3) + 2\text{cov}(\beta_1, \beta_3)$
$= (.424)^2 + (.590)^2 + 2[-.200 (.424)(.590)]$
$= .428$
95% CI = 0.05 - 0.61

Interaction Assessment: Alzheimer's Disease

Interaction Term: HRT*Education

$\ell(h_i, e_{i2}) = \beta_0 + \beta_1 h_{i1} + \beta_2 e_{i1} + \beta_3 e_{i2} + \beta_4 e_{i3} + \beta_5 h_{i1} e_{i1} + \beta_6 h_{i1} e_{i2} + \beta_7 h_{i1} e_{i3} + \beta_{i2}$

For e_1 (6 years or less):

	e_0	e_1	
h_0	β_0	$\beta_0 + \beta_2 e_1$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_2 e_1 + \beta_5 h_1 e_1$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_2$
$= 1.375$
$\text{Exp}(B) = OR = 3.955$

$v(\hat{d}_1) = v(\beta_2)$
$= (1.436)^2 = 2.06$
95% CI = 0.237 - 66.005

$\hat{d}_2 = \beta_2 + \beta_5$
$= 1.375 + (-1.335)$
$= 0.04$
$\text{Exp}(B) = OR = 1.04$

$v(\hat{d}_2) = v(\beta_2) + v(\beta_5) + 2\,\text{cov}(\beta_2, \beta_5)$
$= (1.436)^2 + (1.482)^2 + 2[-.967(1.436)(1.482)]$
$= 0.14$
95% CI = 0.50 - 2.17

$\hat{d}_3 = \beta_1$
$= 2.316$
$\text{Exp}(B) = OR = 10.134$

$v(\hat{d}_3) = v(\beta_3)$
$= (1.047)^2 = 1.09$
95% CI = 1.301 - 78.946

$\hat{d}_4 = \beta_1 + \beta_5$
$= 2.316 + (-1.335)$
$= 0.981$
$\text{Exp}(B) = OR = 2.67$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_5) + 2\,\text{cov}(\beta_1, \beta_5)$
$= (1.047)^2 + (1.482)^2 + 2[-.706(1.047)(1.482)]$
$= 1.11$
95% CI = 0.34 - 21.03

For e_2 (7-9 years):

	e_0	e_2	
h_0	β_0	$\beta_0 + \beta_3 e_2$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_3 e_2 + \beta_6 h_1 e_2$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_3$
$= 2.650$
$\text{Exp}(B) = OR = 14.161$

$v(\hat{d}_1) = v(\beta_3)$
$= (1.102)^2 = 1.21$
95% CI = 1.632 - 122.884

$\hat{d}_2 = \beta_3 + \beta_6$
$= 2.650 + (-2.952)$
$= -0.302$
$\text{Exp}(B) = OR = 0.74$

$v(\hat{d}_2) = v(\beta_3) + v(\beta_6) + 2\text{cov}(\beta_3, \beta_6)$
$= (1.102)^2 + (1.146)^2 + 2[-.957 (1.102)(1.146)]$
$= 0.10$
95% CI = 0.40 - 1.37

$\hat{d}_3 = \beta_1$
$= 2.316$
$\text{Exp}(B) = OR = 10.134$

$v(\hat{d}_3) = v(\beta_3)$
$= (1.047)^2 = 1.09$
95% CI = 1.301 - 78.946

$\hat{d}_4 = \beta_1 + \beta_6$
$= 2.316 + (-2.952)$
$= -0.636$
$\text{Exp}(B) = OR = 0.53$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_6) + 2\text{cov}(\beta_1, \beta_6)$
$= (1.047)^2 + (1.146)^2 + 2[-.917 (1.047)(1.146)]$
$= 0.21$
95% CI = 0.22 - 1.30

For e_3 (10-12 years):

	e_0	e_3	
h_0	β_0	$\beta_0 + \beta_4 e_3$	$\hat{d}_1$
h_1	$\beta_0 + \beta_1 h_1$	$\beta_0 + \beta_1 h_1 + \beta_4 e_3 + \beta_7 h_1 e_3$	$\hat{d}_2$
	$\hat{d}_3$	$\hat{d}_4$	

$\hat{d}_1 = \beta_4$
$= 1.501$
$\text{Exp}(B) = OR = 4.485$

$v(\hat{d}_1) = \beta_4$
$= (1.113)^2$
$= 1.24$
95% CI = 0.506 – 39.752

$\hat{d}_2 = \beta_4 + \beta_7$
$= 1.501 + (-1.932)$
$= -.431$
$\text{Exp}(B) = OR = 0.65$

$v(\hat{d}_2) = v(\beta_4) + v(\beta_7) + 2\,\text{cov}(\beta_4, \beta_7)$
$= (1.113)^2 + (1.152)^2 + 2[-.965(1.113)(1.152)]$
$= 0.10$
95% CI = 0.35 – 1.21

$\hat{d}_3 = \beta_1$
$= 2.316$
$\text{Exp}(B) = OR = 10.134$

$v(\hat{d}_3) = v(\beta_1)$
$= (1.047)^2$
$= 1.09$
95% CI = 1.301 – 78.946

$\hat{d}_4 = \beta_1 + \beta_7$
$= 2.316 + (-1.932)$
$= 0.384$
$\text{Exp}(B) = OR = 1.47$

$v(\hat{d}_4) = v(\beta_1) + v(\beta_7) + 2\,\text{cov}(\beta_1, \beta_7)$
$= (1.047)^2 + (1.152)^2 + 2[-.901(1.047)(1.152)]$
$= 0.25$
95% CI = 0.55 – 3.91